Viral hepatitis in reproductive health

Pierre Jean Malè

Training in Reproductive Health Research - Geneva 2006

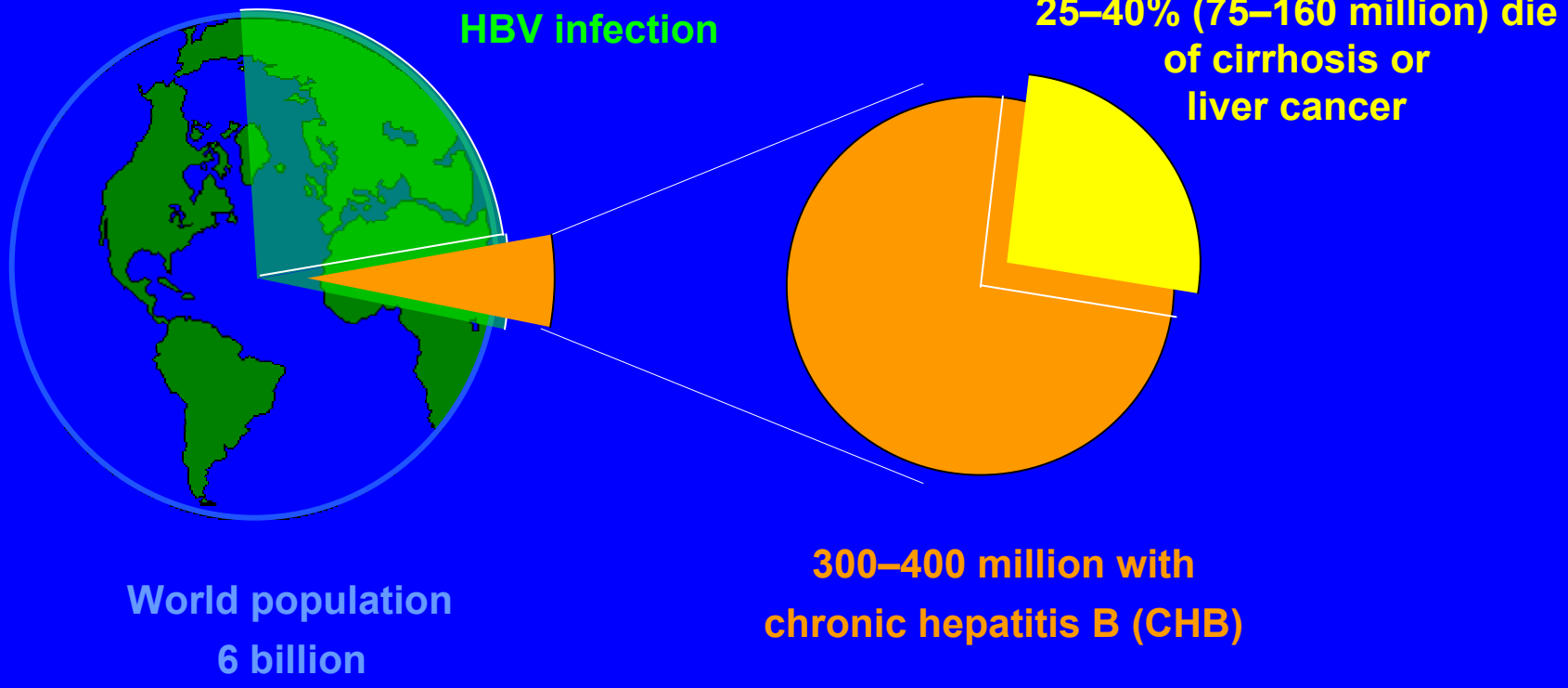
15.03.2006

HBV and HCV treatment

Pierre-Jean Malè MD

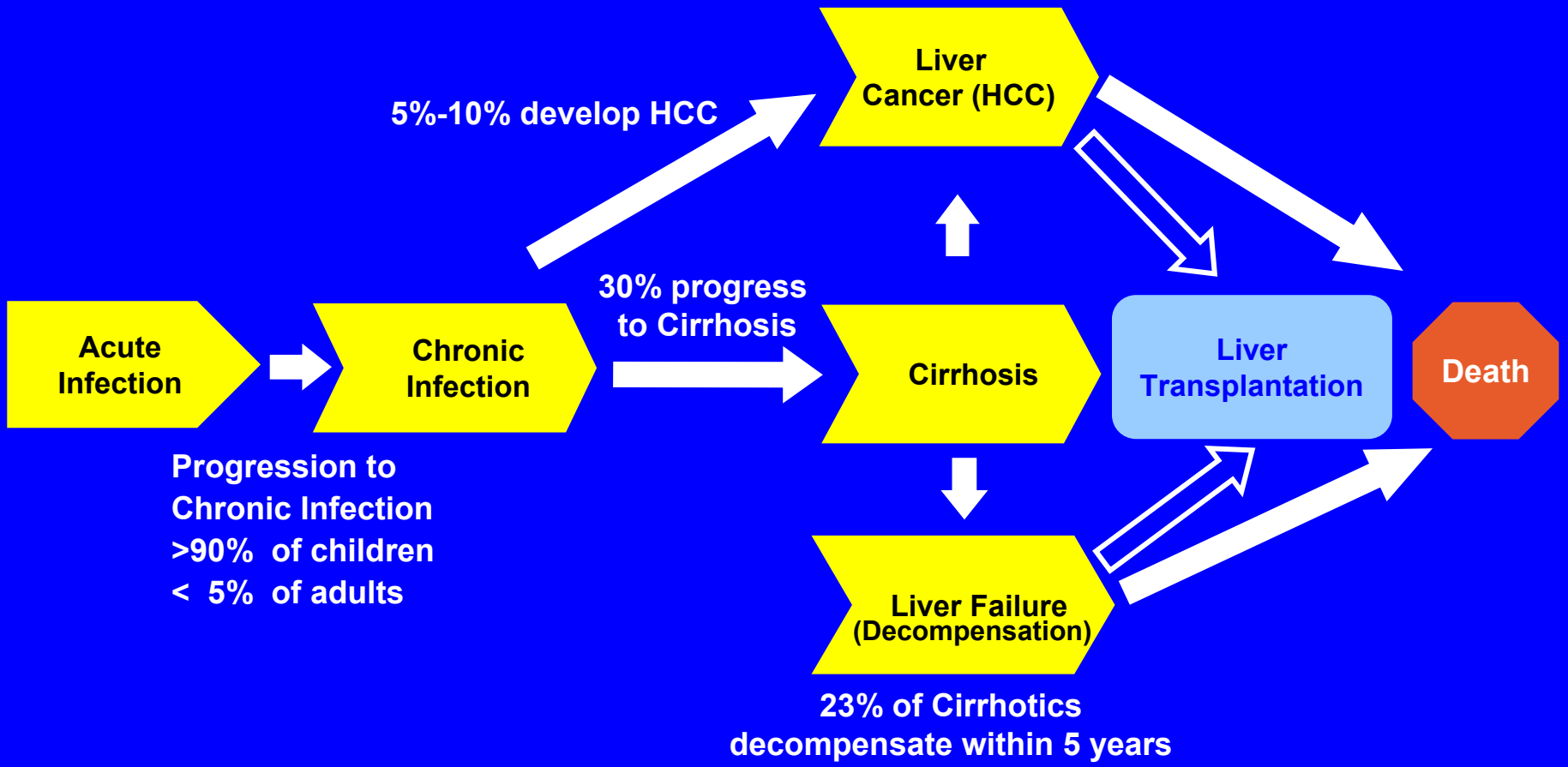
15.03.2006

Global Impact of Hepatitis B



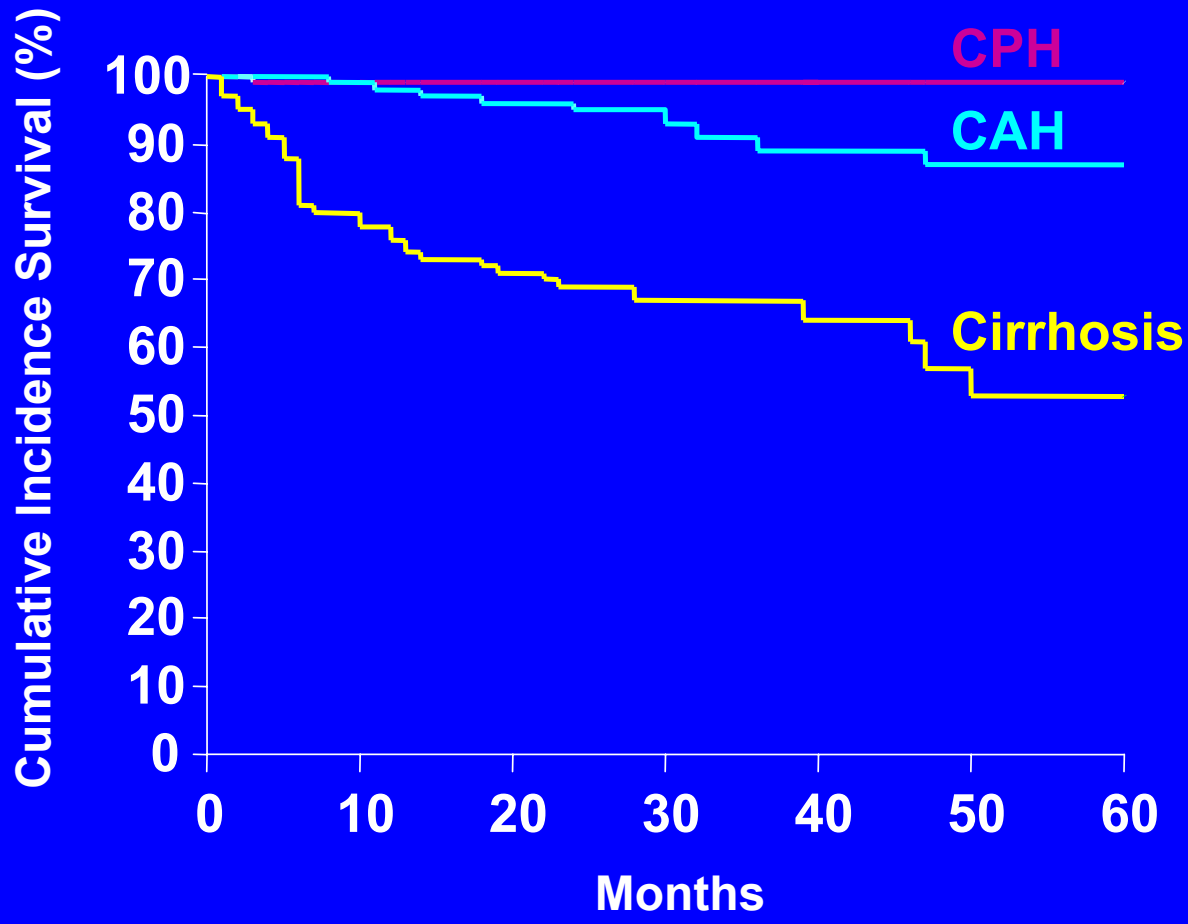
WHO and CDC Fact Sheets

Hepatitis B Disease Progression



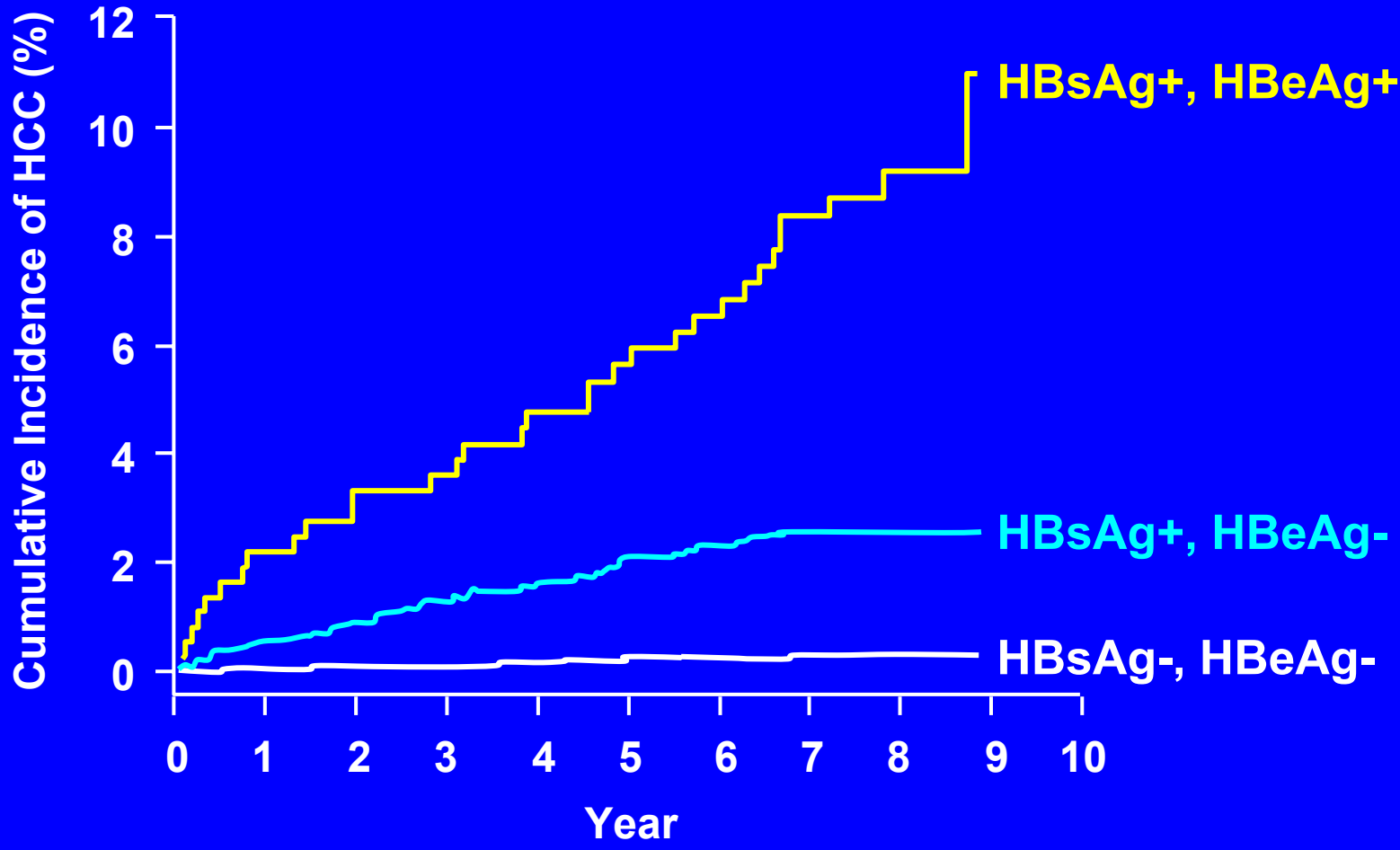
Torresi, J, Locarnini, S. Gastroenterology. 2000.
Fattovich, G, Giustina, G, Schalm, SW, et al. Hepatology. 1995. ; Moyer, LA, Mast, EE. Am J Prev Med. 1994.

5 Year Survival in Chronic Hepatitis B



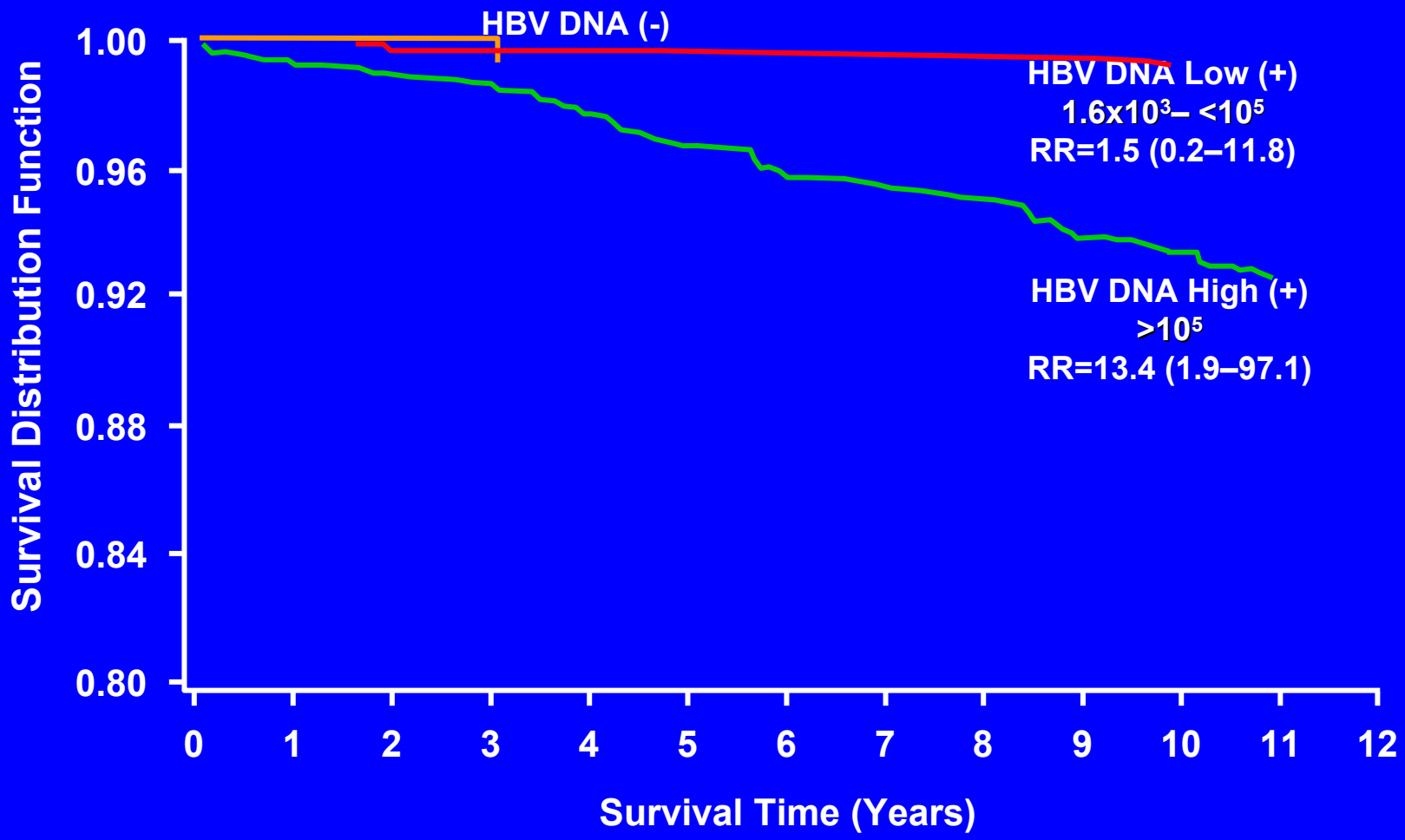
Weissberg, JI, et al. Ann Intern Med. 1984;101:613-616.

Hepatitis B and Risk of HCC



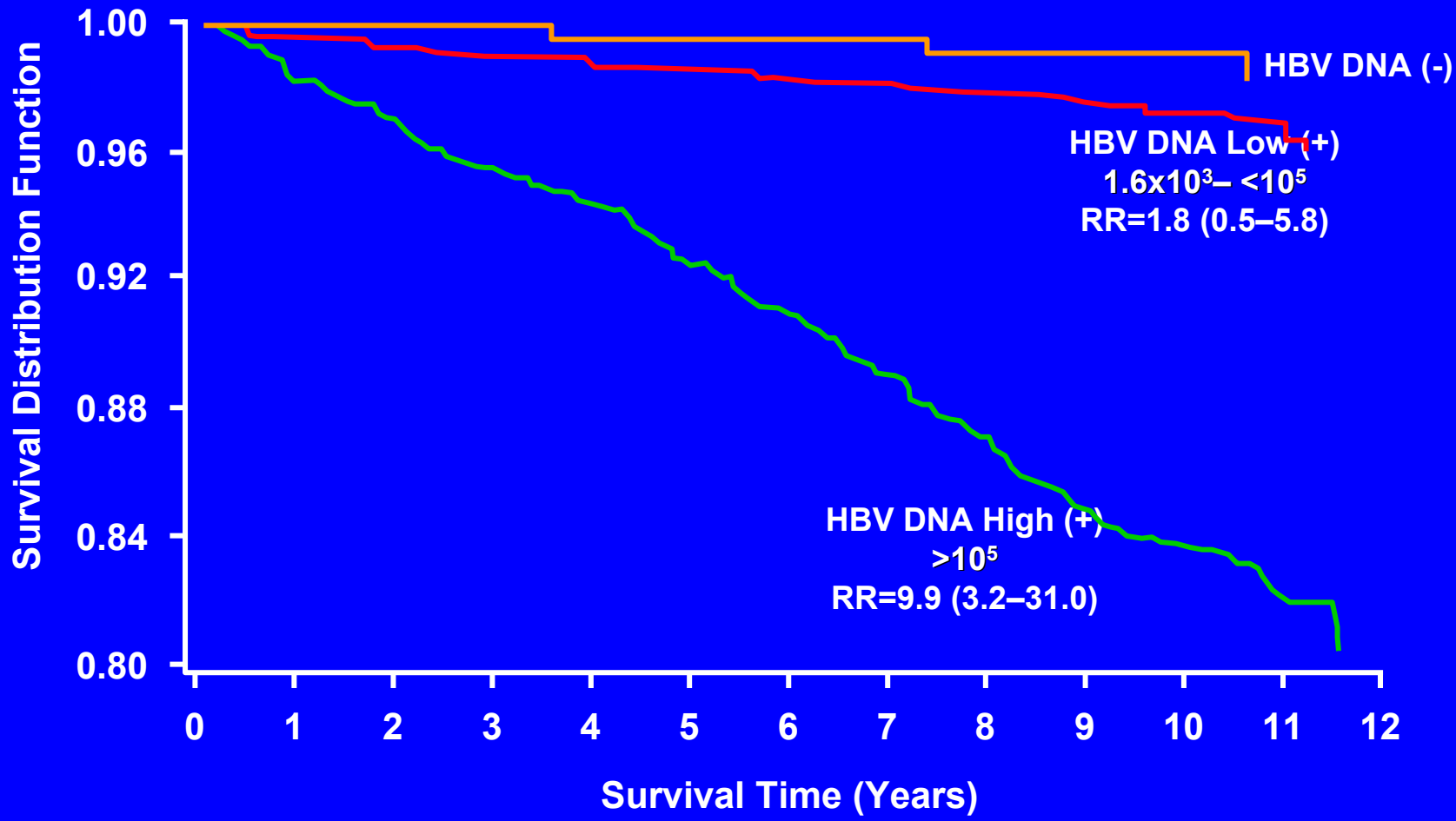
Yang, HI, et al. N Engl J Med. 2002;347:168-174.

Chronic Liver Disease Mortality by HBV Viral Load at Baseline



Chen G et al 55th AASLD Boston MA Nov 2004; Poster 1362

HCC Mortality by HBV Viral Load at Baseline



Chen G et al 55th AASLD Boston MA Nov 2004; Poster 1362

Active-passive Hepatitis B immunization

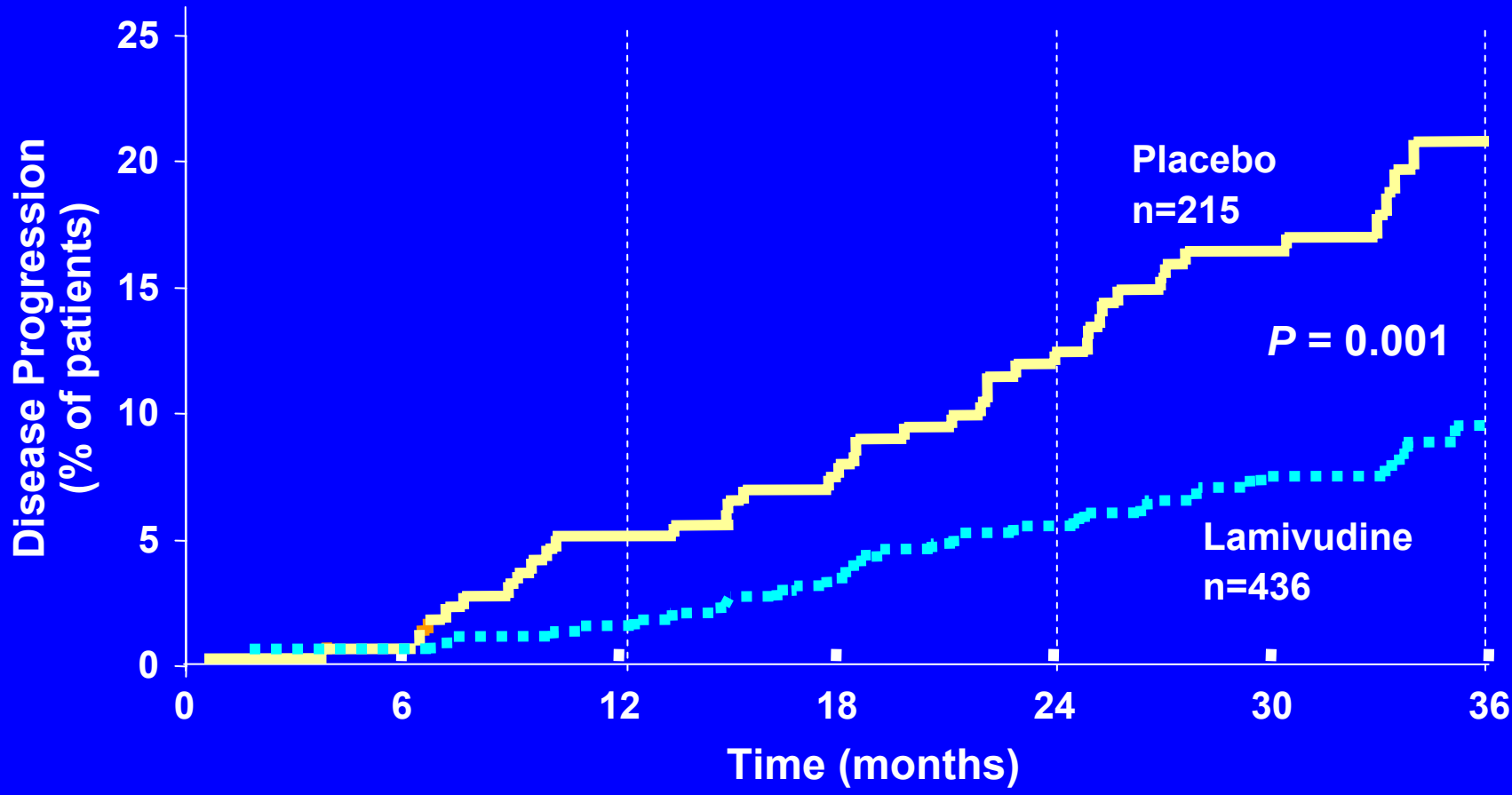
- *prevention is the best way to control hepatitis B*
- *active-passive immunization successful in 95 % of the children*
- *hepatitis B immunization is a cancer vaccine in reducing the incidence of HCC to 1/4-1/3 of that in children born before the hepatitis B vaccination era in Taiwan*
- *pregnant women must be checked for HBV markers*

Goals of Treatment

- Eliminate or significantly suppress HBV replication
- Prevent progression of liver disease to cirrhosis and liver failure
- Prevention of HCC
- Improve survival
- Treatment endpoints
  - Normalize ALT
  - Decrease HBV DNA
  - Induce HBeAg loss and seroconversion
  - Improve histology
  - Prevent and/or reverse decompensation

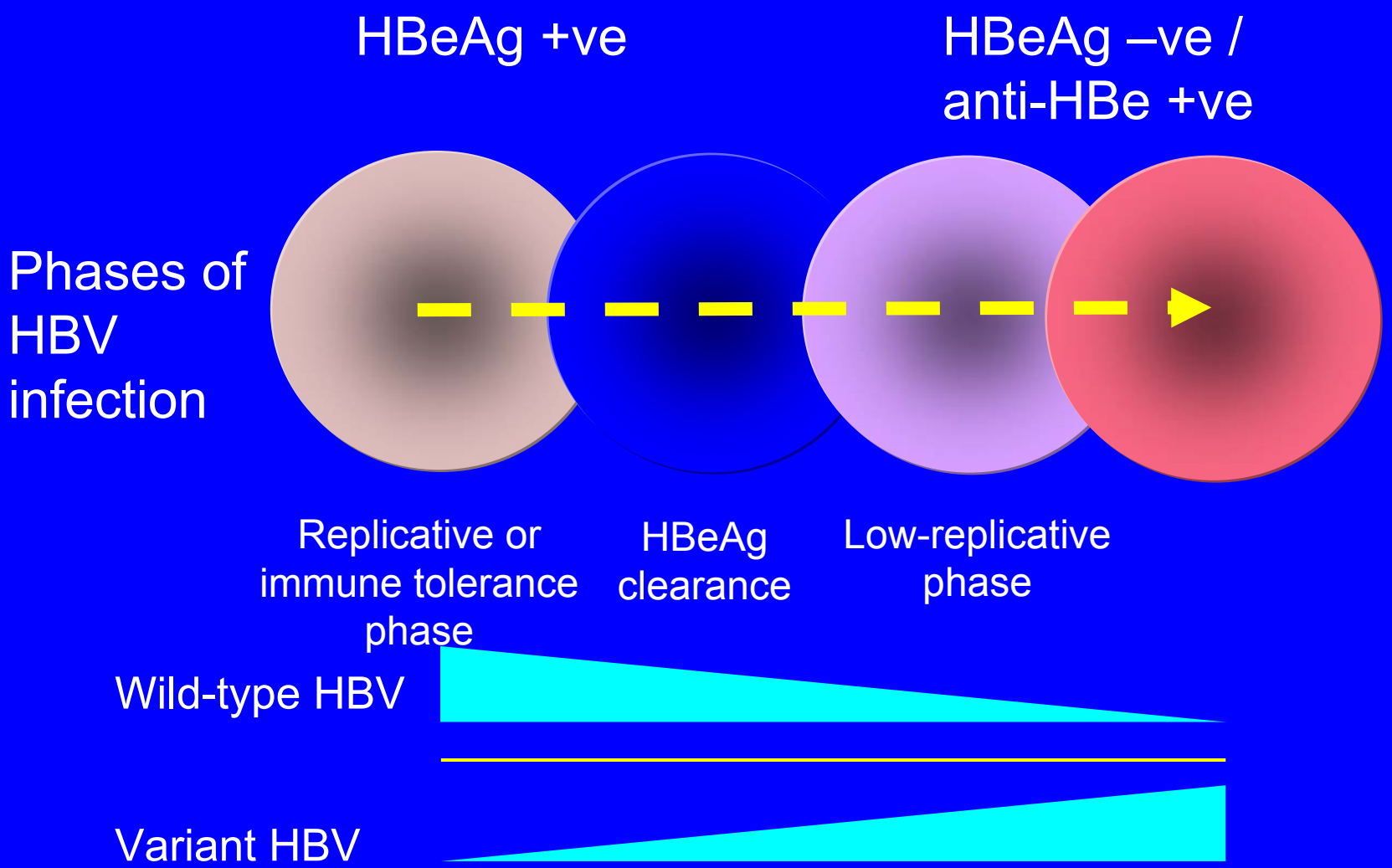
Keeffe et al., Clinical Gastroenterology and Hepatology 2004; 2:87-106.
Conjeevaram HS. J Hepatol. 2003;38:S90-S103

Effective Treatment May Slow Disease Progression



Adapted from Liaw et al. *N Engl J Med.* 2004;351:1521-1531.

Natural Course of Chronic HBV Infection



Brunetto *J Hepatol* 1991

Treatment of hepatitis B: whom?

- Acute hepatitis B
  - ➔ usually not indicated
- Inactive carrier
  - ➔ not indicated (except in case of prophylaxis of reactivation before chemotherapy)

- Chronic hepatitis B, HBeAg+
  - ➔ if HBV DNA $>10^5$ **and** disease
- Chronic hepatitis B, HBeAg-
  - ➔ if HBV DNA $>10^4$ **and** disease

KEEFFE et al, 2004

Recommendations for Treatment

	EASL 2003		AASLD 2004		Keeffe Algorithm 2004*	
HBeAg +						
HBV DNA	> 10^5 copies/mL		> 10^5 copies/mL		≥ 10^5 copies/mL	
ALT	N or <2xULN	No	≤ 2x ULN	No	Normal	if disease
	> 2x ULN	Yes	> 2x ULN	Yes	Elevated	Yes
HBeAg-						
HBV DNA	< 10^5 copies/mL		< 10^5 copies/mL		< 10^4 copies/mL	
ALT	N or < 2xULN	No	≤ 2 x ULN	No	Normal	No
HBV DNA	> 10^5 copies/mL >		> 10^5 copies/mL		≥ 10^4 copies/mL	
ALT	2x ULN	Yes	> 2x ULN	Yes	Normal	if disease
					Elevated	Yes

* Keeffe et al. Clinical Gastroenterology and Hepatology, 2004; 2:87-106

Current Treatment Options

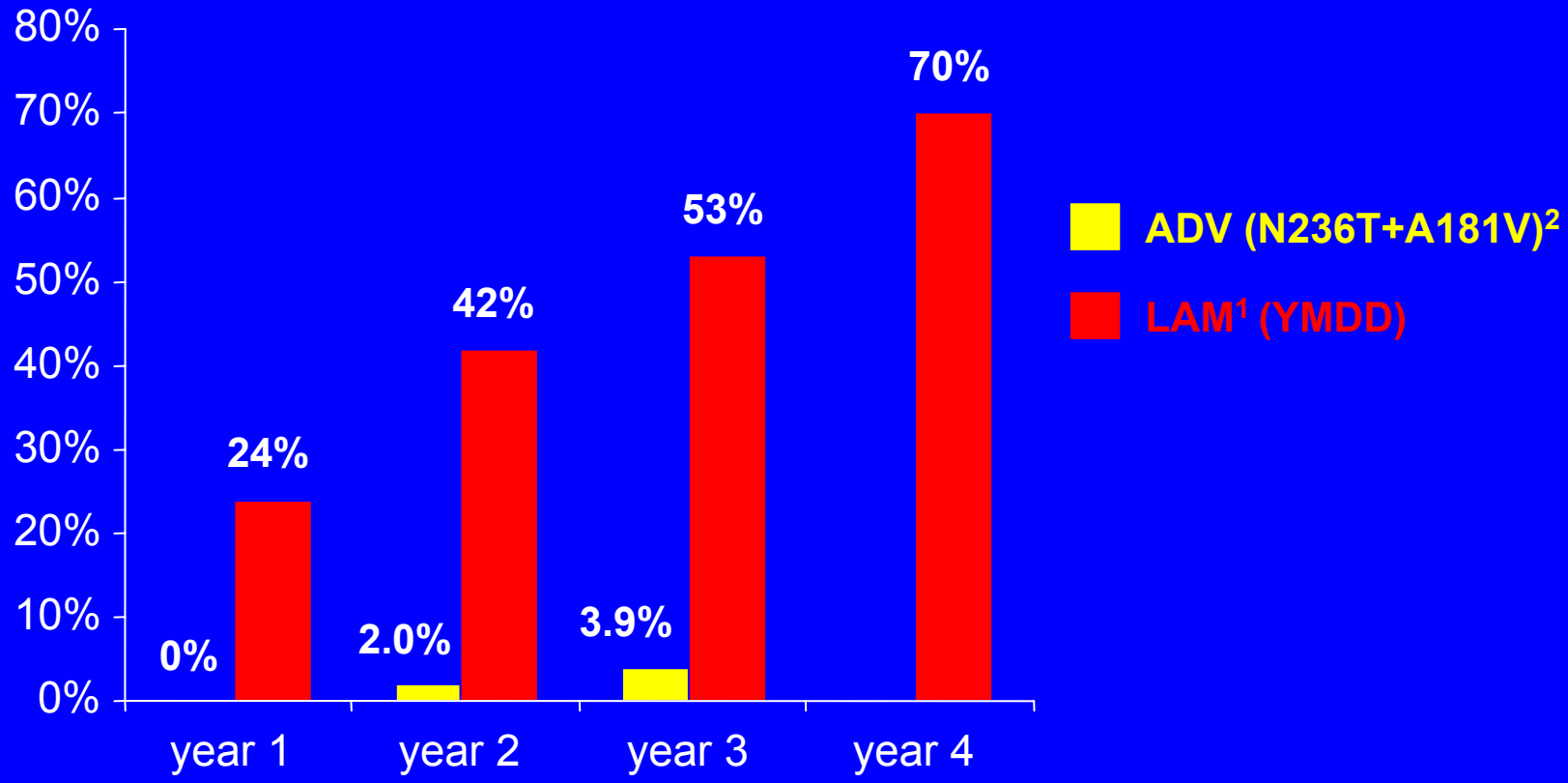
	Strengths	Weaknesses
Lamivudine	• Oral • Negligible side effects	• Long /indefinite therapy • Significant rate of resistance with long term therapy
Adefovir	• Oral • Effective against wild-type and LVD resistant HBV • Low rate of resistance	• Long /indefinite therapy • Moderate viral load reduction
Interferon	• Finite duration of treatment • Durable post-treatment response • No report of resistant mutations	• Injection • Side effects frequently reported

Adapted from Lok ASF. HBV Treatment Guidelines: Questions and Controversies http://clinicaloptions.com/hep/conf/ccohep2004/. Accessed: December 9, 2004.
EASL Consensus Conference, J Hepatol, 2003

Integrated Resistance Surveillance Across ADV Studies (0-144 weeks)

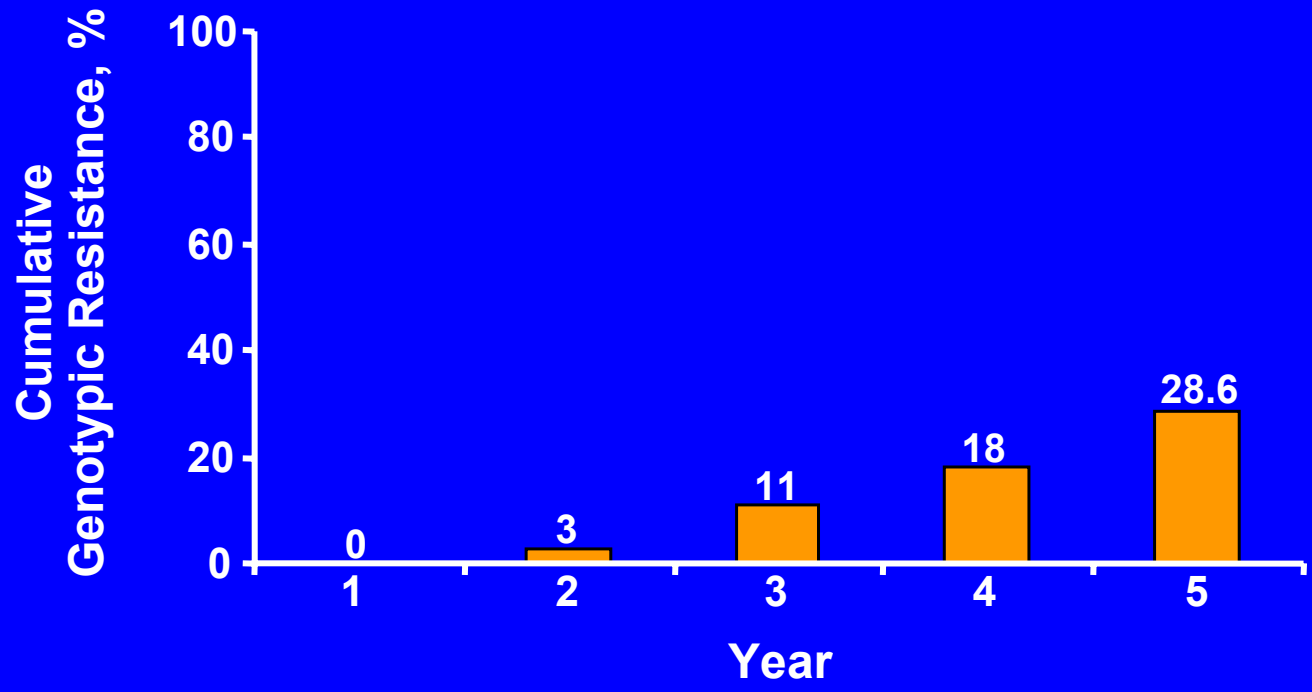
Incidence of ADV Compared to Lamivudine Resistance

- Delayed and infrequent emergence of adefovir resistance mutations



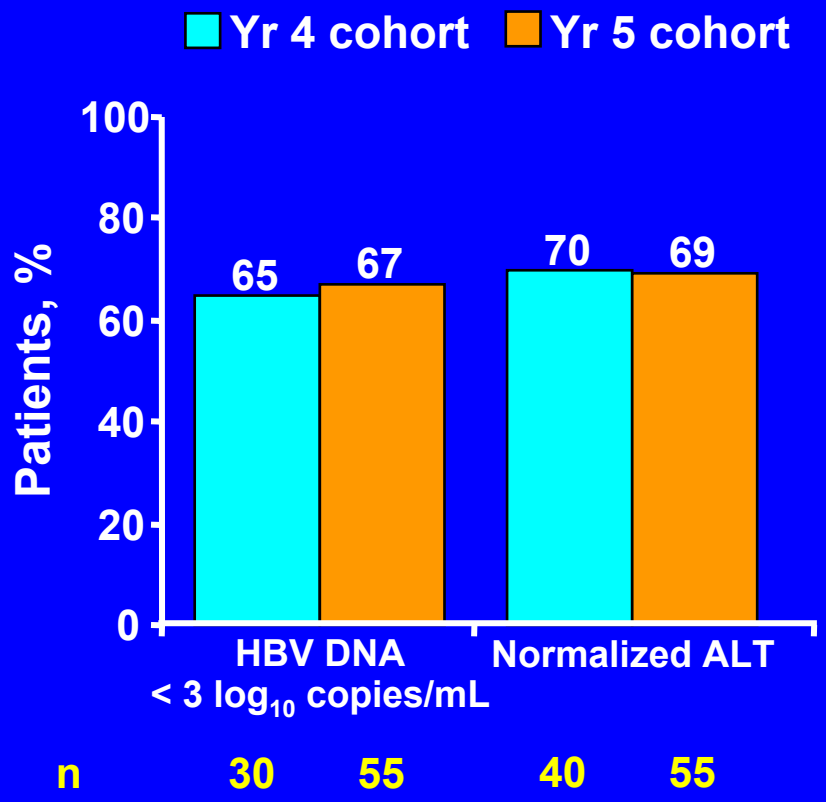
Long-Term Data on Treatment With Adefovir in HBeAg-Negative Patients

- Cumulative genotypic resistance by Year 5, 28.6%
- 4 (3%) by Yr 5 had increase in creatinine of ≥ 0.5 mg/dL



Hadziyannis et al. AASLD 2005. Abstract LB14.

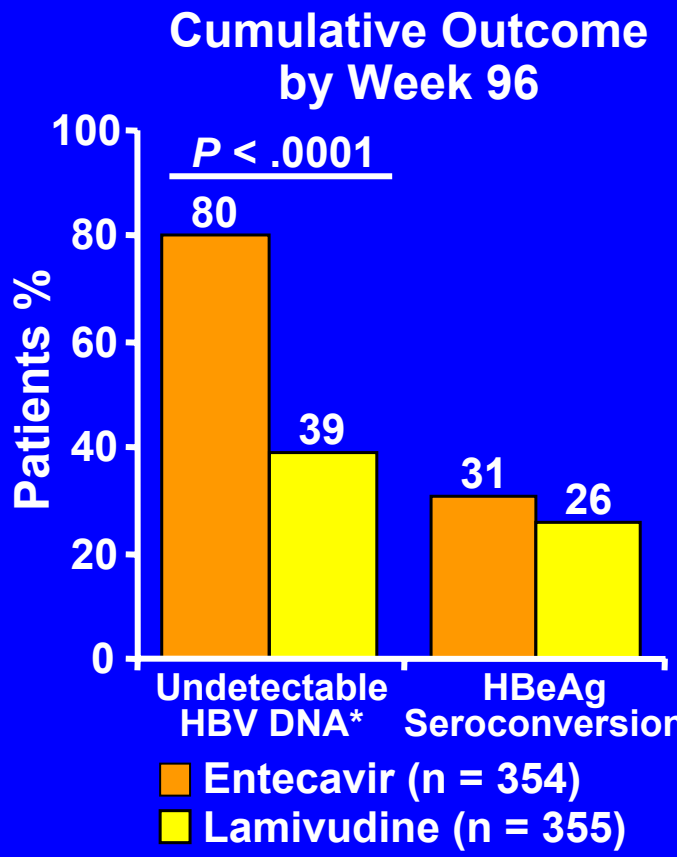
Long-Term Data on Treatment With Adefovir in HBeAg-Negative Patients

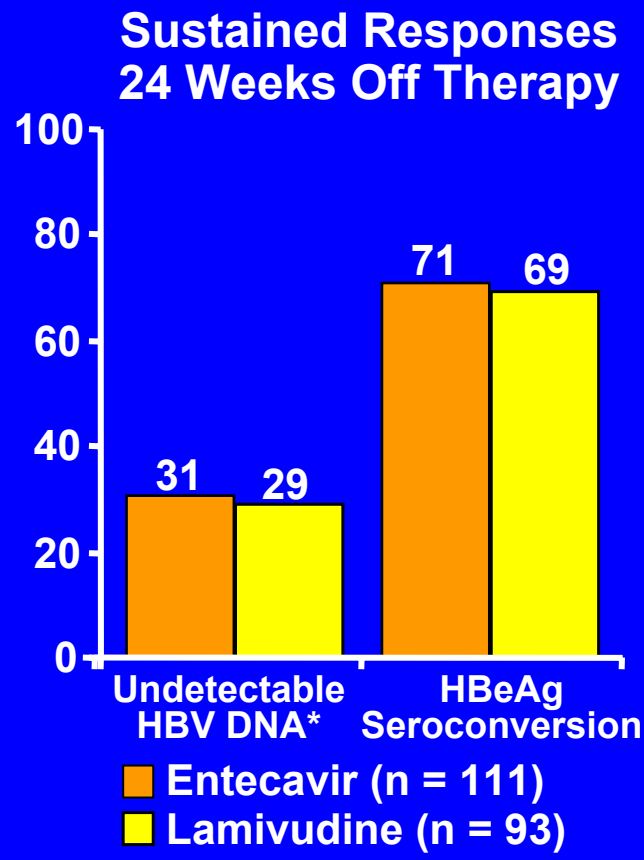


- > 5% of patients had HBsAg loss by Year 5
- 50% had regression of bridging fibrosis or cirrhosis by Year 5
- ≥ 1-point reduction in Ishak fibrosis score
  - Year 4 cohort, 55%
  - Year 5 cohort, 71%

Hadziyannis et al. AASLD 2005. Abstract LB14.

ETV-022: HBeAg-Positive Patients Treated Up to 96 Wks With Entecavir

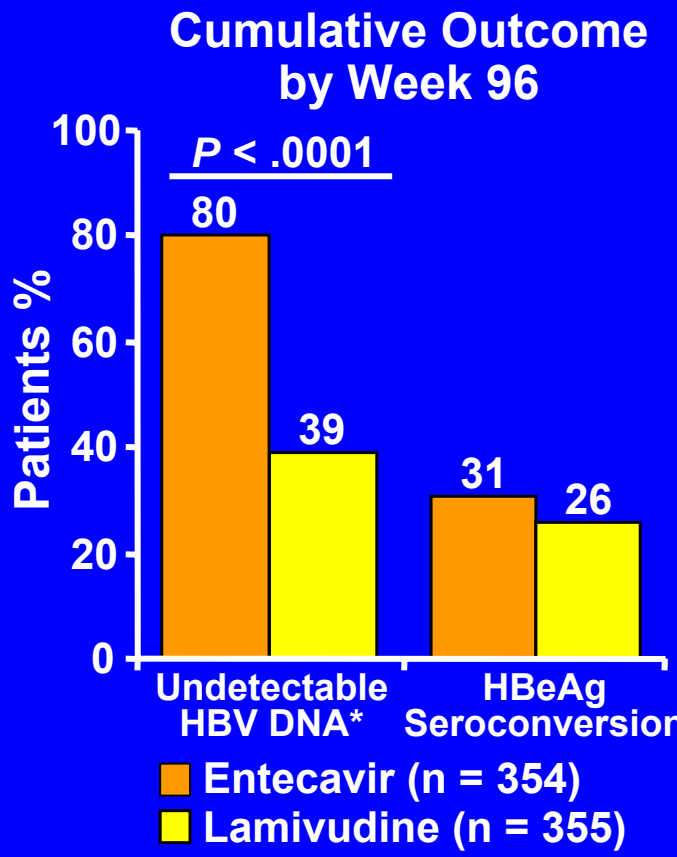


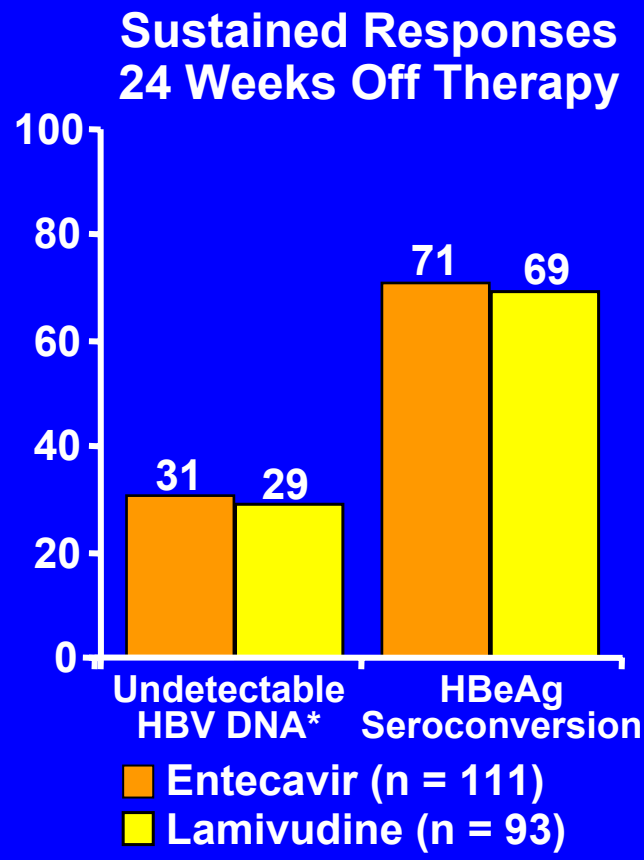


**Undetectable HBV DNA, < 300 copies/mL*

Gish et al. AASLD 2005. Abstract 181.

ETV-022: HBeAg-Positive Patients Treated Up to 96 Wks With Entecavir





**Undetectable HBV DNA, < 300 copies/mL*

Gish et al. AASLD 2005. Abstract 181.

Nucleoside/Nucleotide Analogues

Compound	Activity	Company	Status
Lamivudine	HIV, HBV	GlaxoSmithKline	Approved for HBV 1998
Adefovir	HIV, HBV	Gilead	Approved for HBV 2002 US 2003 Europe
Entecavir	HBV only	Bristol-Myers Squibb	Approved 2005 US Not currently approved elsewhere in the world
Emtricitabine	HIV, HBV	Gilead	Approved for HIV In development for HBV
Telbivudine	HBV only	Idenix/Novartis	In development for HBV
Tenofovir	HIV; HBV	Gilead	Approved for HIV In development for HBV

AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

AASLD

2004 AASLD
Annual Meeting

Peginterferon alfa-2a (40KD) (PEGASYS®) Monotherapy and in Combination with Lamivudine is More Effective than Lamivudine Monotherapy in HBeAg-positive Chronic Hepatitis B: Results from a Large, Multinational Study

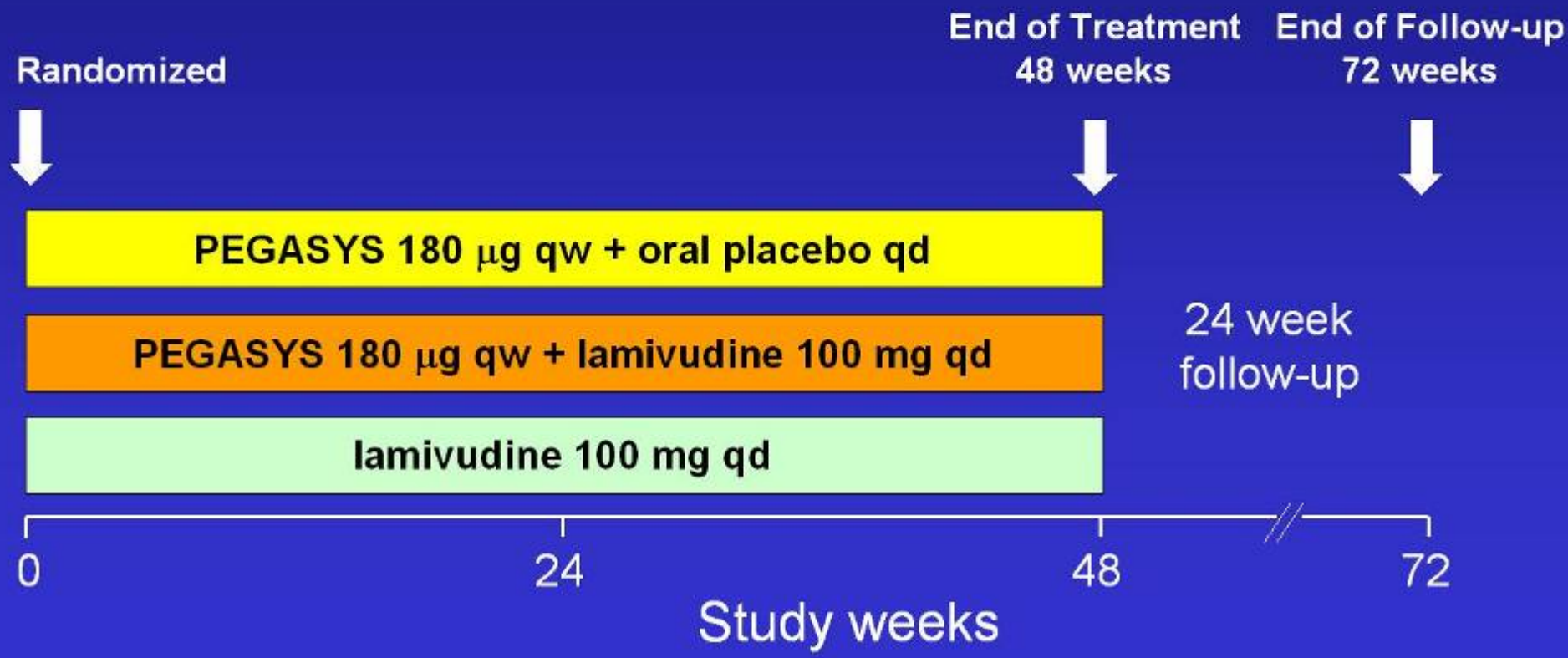
Professor George K. K. Lau
Hong Kong

I have financial relationships with commercial entities and the content of my presentation does include discussion of off-label/investigative use of medicine(s), medical devices, or procedures.
[Consultant and lecturer for Roche]

Study Design

Patients with HBeAg-positive CHB were randomized using a 1:1:1 ratio

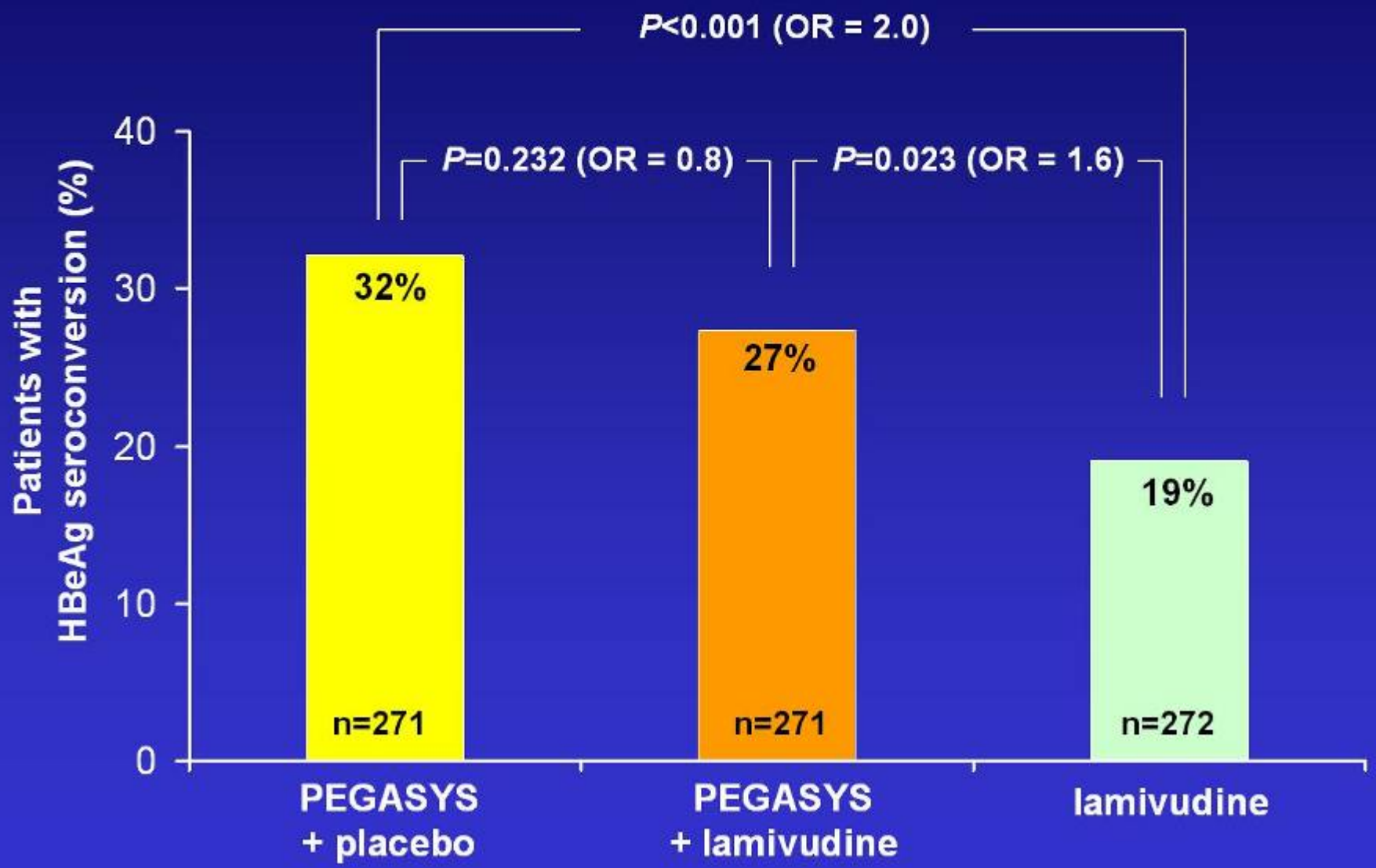
ITT population: n=814



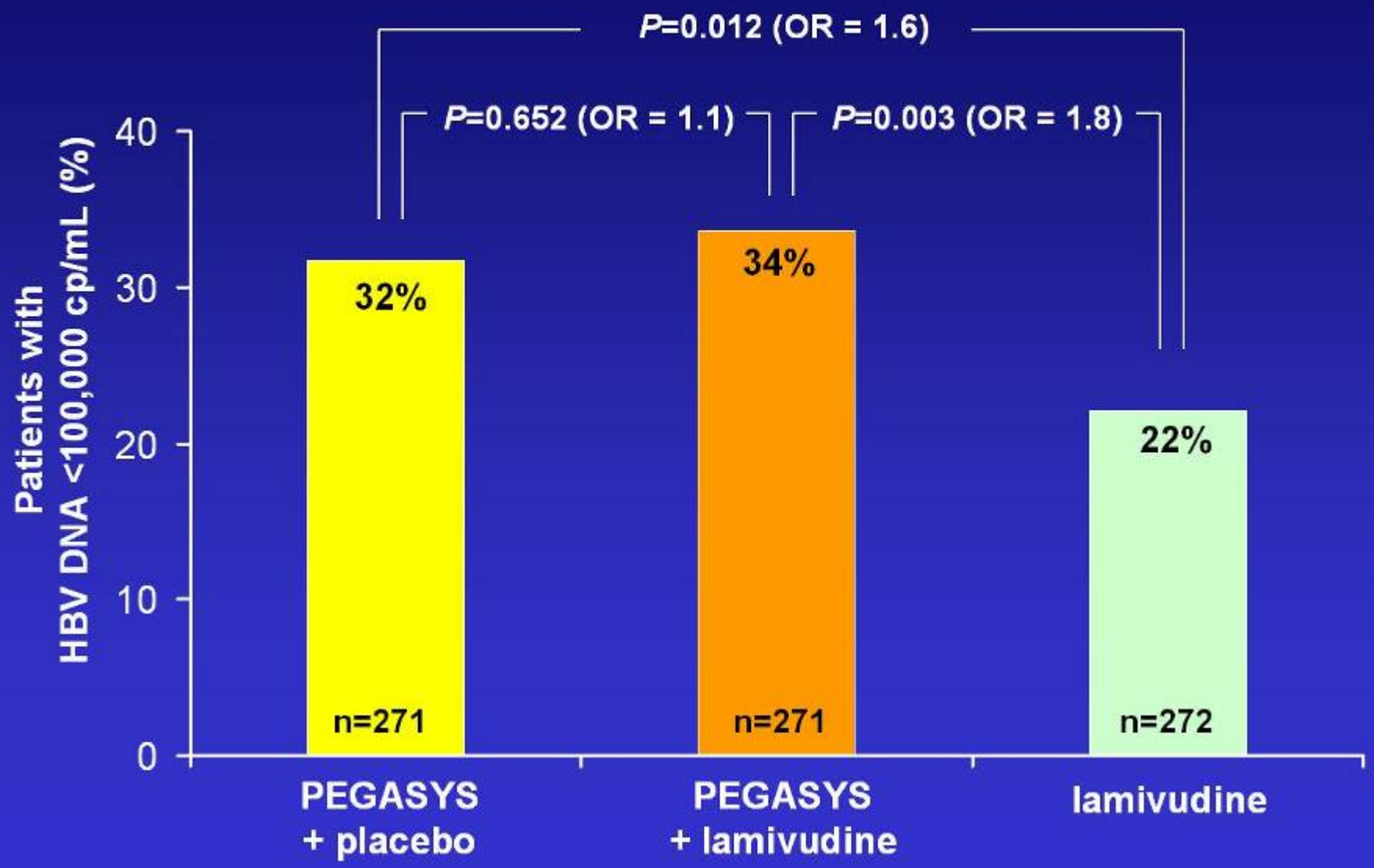
Key Inclusion Criteria

- HBsAg-positive for >6 months
- HBeAg-positive
- anti-HBs-negative
- HBV DNA >500,000 cp/mL
  (COBAS AMPLICOR HBV MONITOR®)
- Serum ALT >1, but ≤10 x ULN at screening
  - <20% with serum ALT 1–2 x ULN
- Liver biopsy proven CHB
  - Maximum 30% with bridging fibrosis/cirrhosis

HBeAg Seroconversion at End of Follow-up (Week 72)



HBV DNA <100,000 cp/mL at End of Follow-up (Week 72)



HBsAg Loss and Seroconversion* at End of Follow-up (Week 72)

	PEGASYS + placebo (n=271)	PEGASYS + lamivudine (n=271)	lamivudine (n=272)
HBsAg loss, n (%)	9 (3%)	11 (4%)	2 (<1%)
HBsAg seroconversion, n (%)	8 (3%)	8 (3%)	0 (0%)

P=0.012

P=0.033

P=0.004

P=0.004

* loss of HBsAg and presence of anti-HBs

Peginterferon alfa-2a (40KD) (PEGASYS®) monotherapy is more effective than lamivudine monotherapy in the treatment of HBeAg-negative chronic hepatitis B

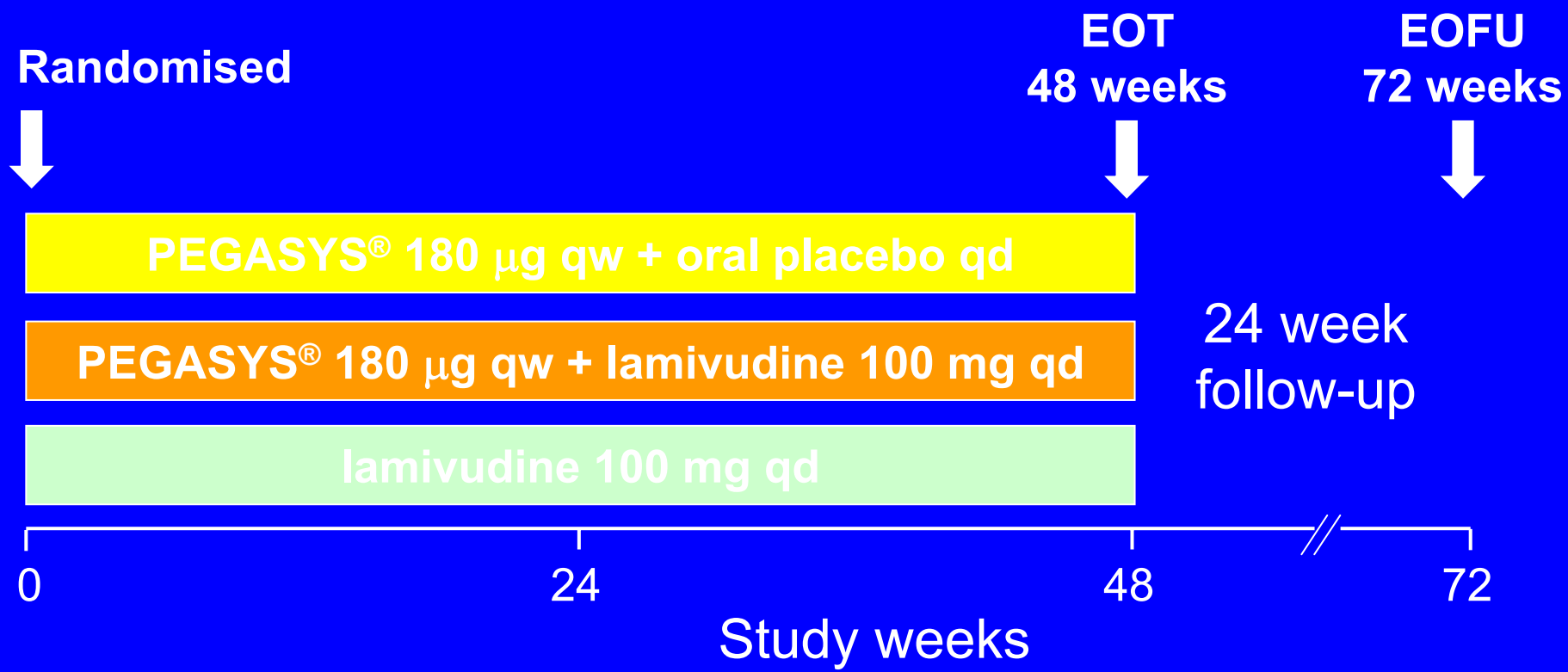
72-week results from a Phase III, partially double-blind study

P Marcellin, GKK Lau, F Bonino, P Farci, S Hadziyannis, R Jin, Z-M Lu, T Piratvisuth, G Germanidis, N Pluck

Study Design

Patients with HBeAg-negative CHB were randomised using a 1:1:1 ratio

ITT population: n=537



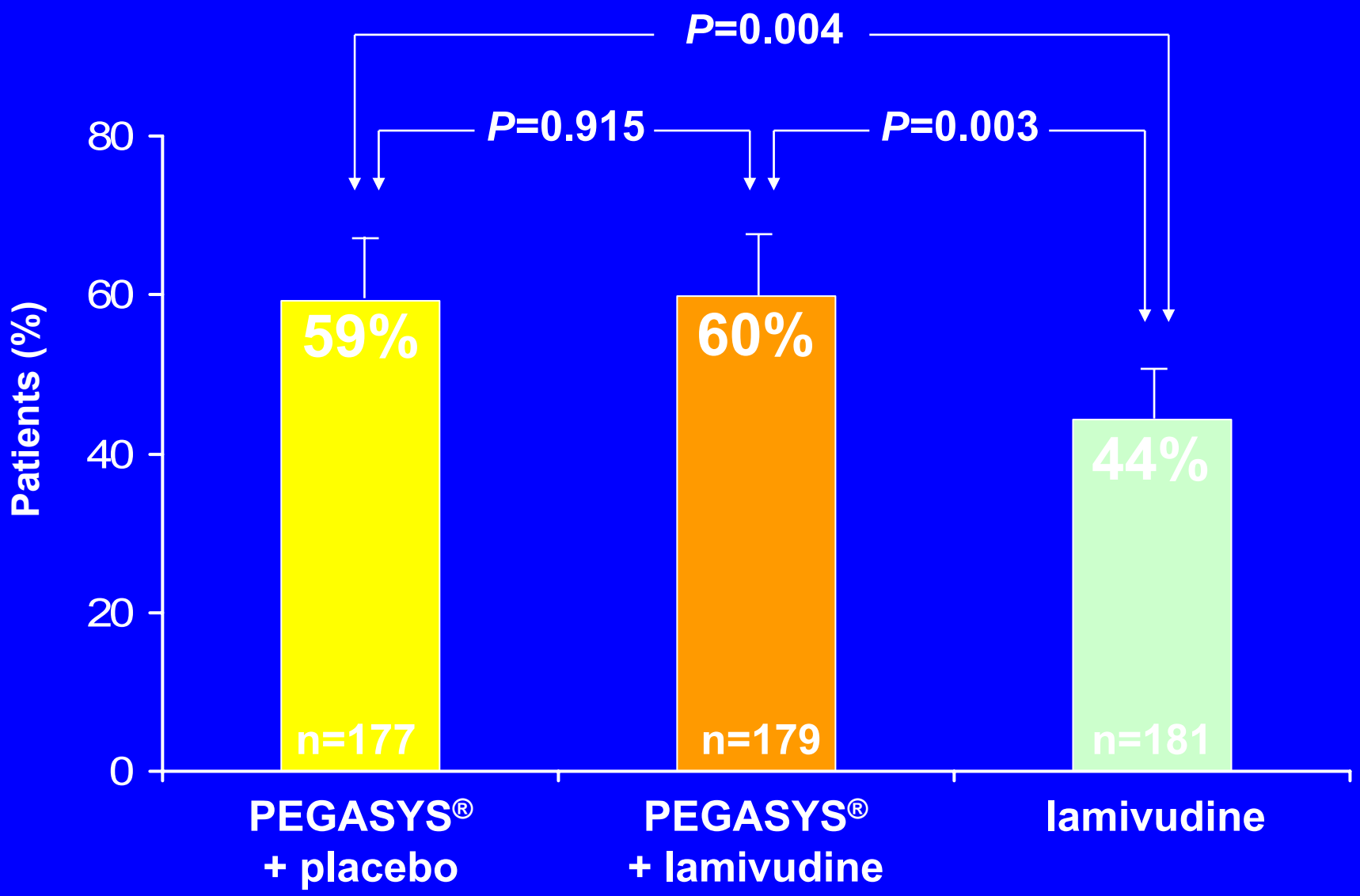
Key Inclusion Criteria

- **HBsAg positive for ≥6 months**
- **HBeAg negative, anti-HBe positive for ≥6 months**
- **HBV DNA >100,000 cp/mL**
  (COBAS AMPLICOR HBV MONITOR®)
- **Serum ALT >1 but ≤10 x ULN at screening**
  - **Less than 20% with serum ALT 1–2 x ULN**
- **Liver biopsy proven CHB**

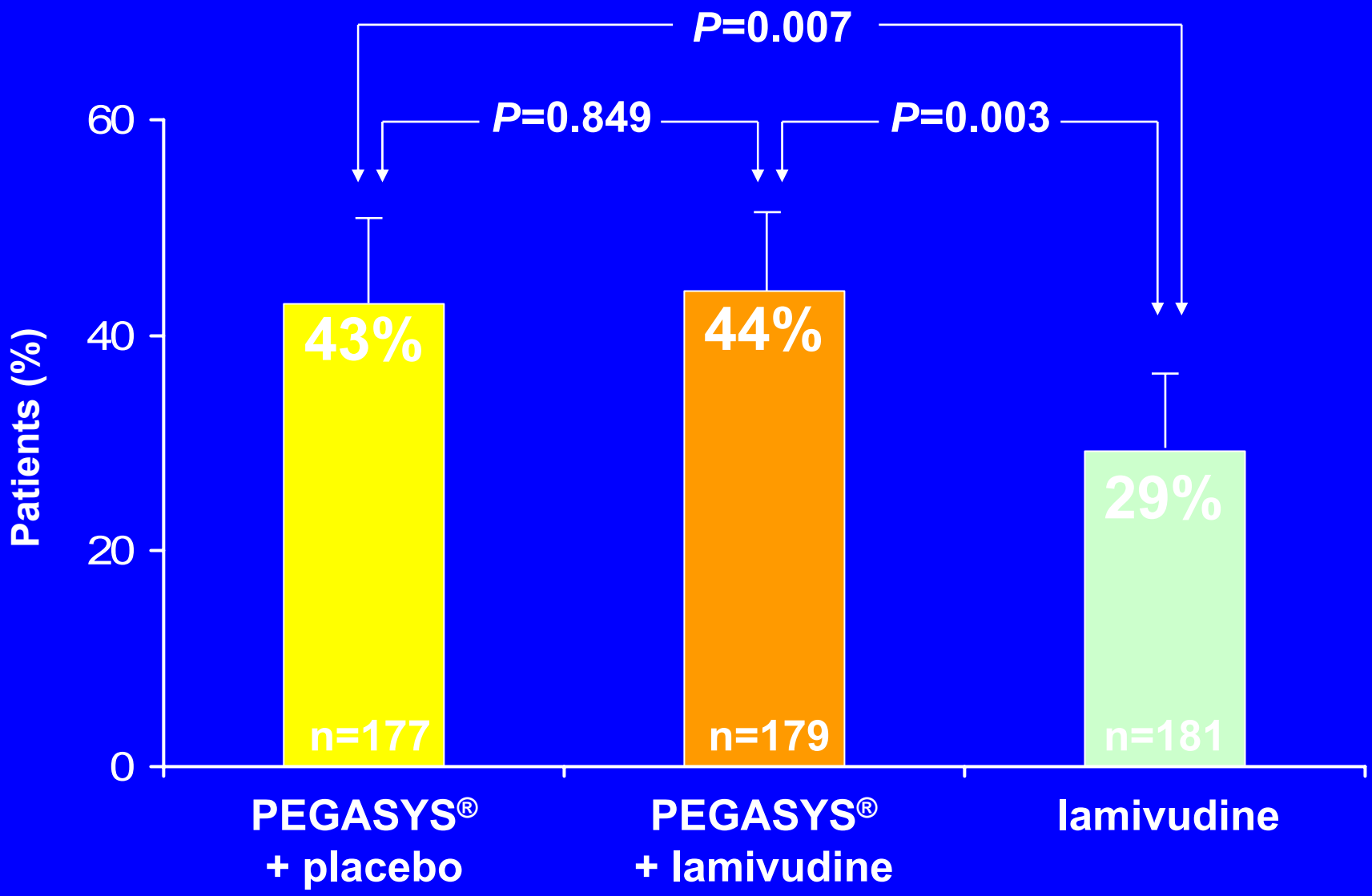
Study Endpoints

- **Co-primary endpoints**
  - **Normal ALT (≤1 x ULN) at end of follow-up**
  - **HBV DNA <20,000 cp/mL at end of follow-up (COBAS AMPLICOR HBV MONITOR®)**
- **Secondary endpoints**
  - **HBV DNA over time**
  - **Histology at end of follow-up (Ishak)**
  - **HBsAg loss/seroconversion at end of follow-up**

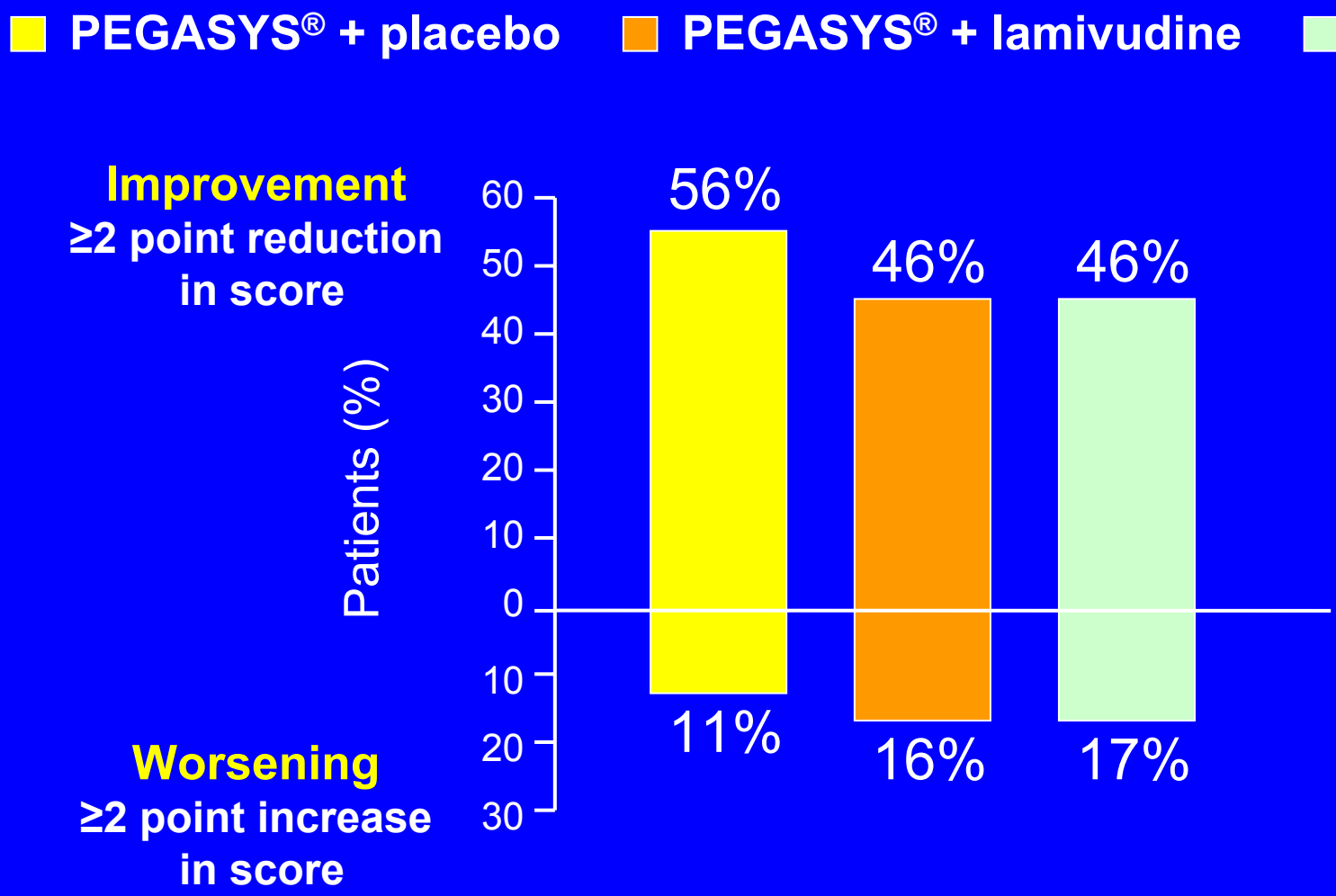
Normal ALT at End of Follow-up (Week 72)



HBV DNA <20,000 cp/mL at End of Follow-up (Week 72)



Necroinflammatory Activity at End of Follow-up (Week 72): Patients with Paired Biopsy

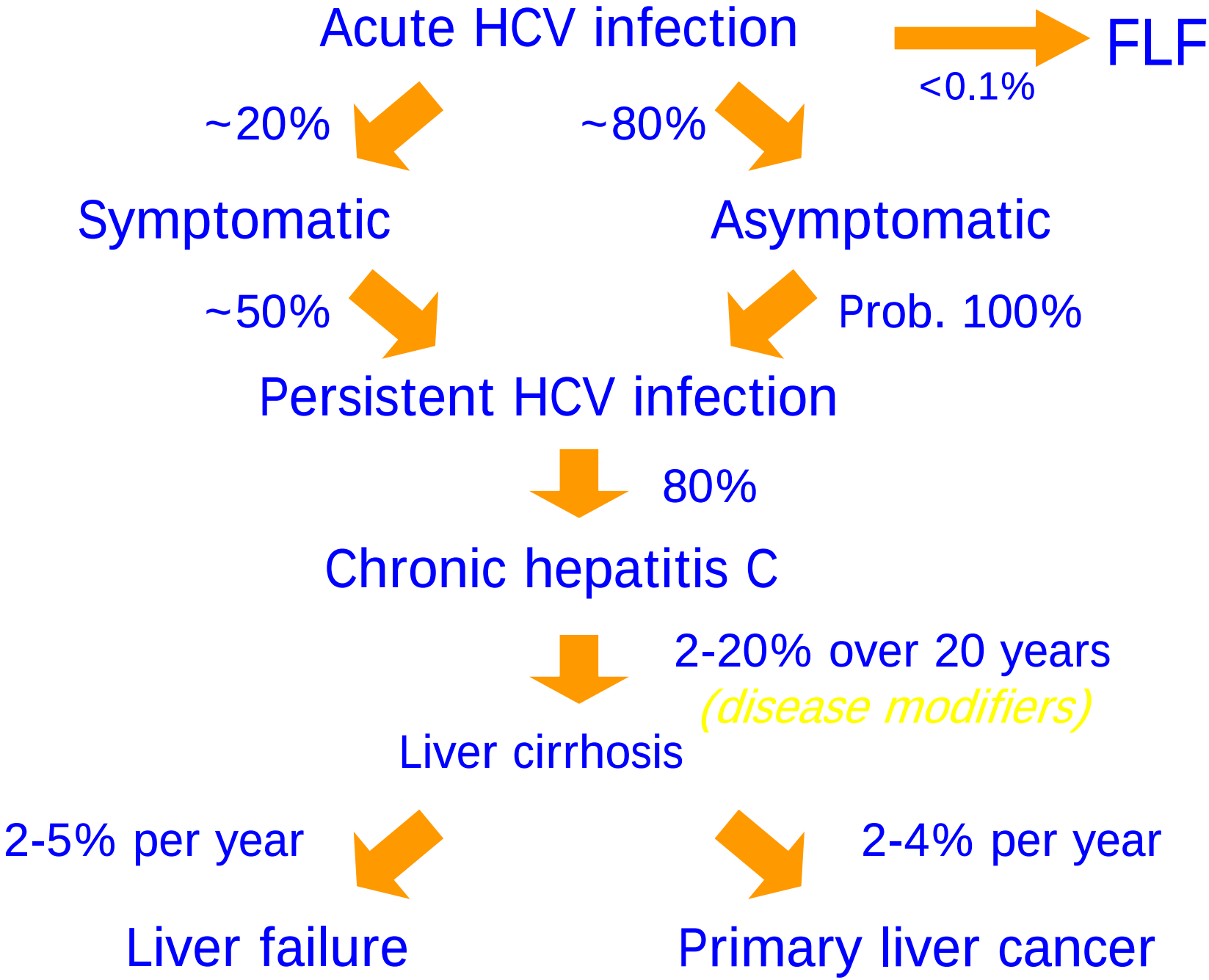


HBsAg Loss and Seroconversion at End of Follow-up (Week 72)

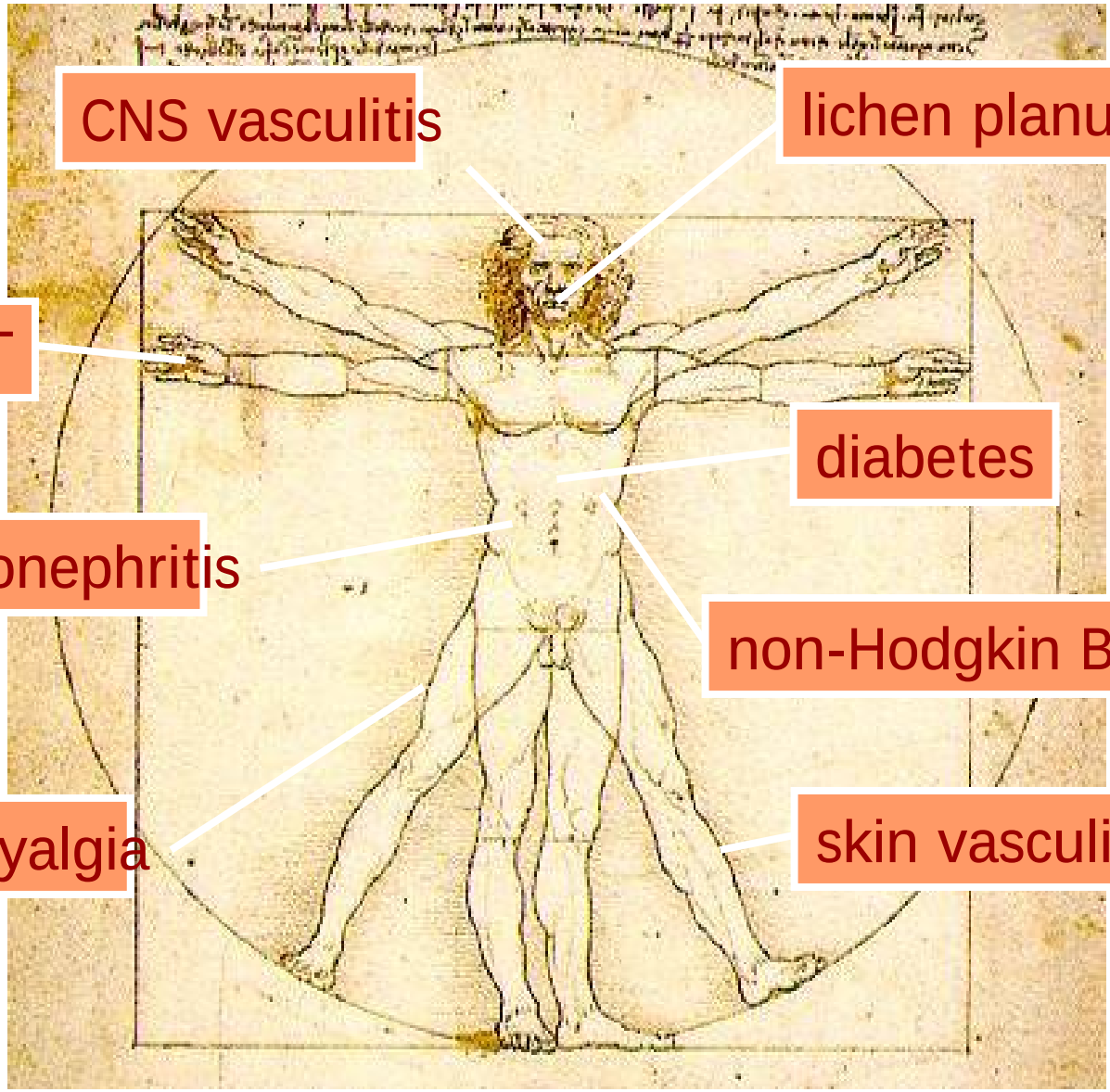
	PEGASYS® + placebo (n=177)	PEGASYS® + lamivudine (n=179)	lamivudine (n=181)
HBsAg loss, n (%)	7 (4%)	5 (3%)	0 (0%)
			P=0.007
‘s’ seroconversion, n (%)	5 (3%)	3 (2%)	0 (0%)
			P=0.029

Treatment of hepatitis B: conclusions

- Many hepatitis B patients will progress spontaneously to inactive carriership
- Current therapy aims at accelerating the natural history of HBV infection towards progression to inactive carriership
- The efficacy of current regimens depends on the competence of the host adaptive immune response to HBV antigens
- Seroconversion to anti-HBs is still very rare


Acute HCV infection
FLF
<0.1%
~20%
~80%
Symptomatic
Asymptomatic
~50%
Prob. 100%
Persistent HCV infection
80%
Chronic hepatitis C
2-20% over 20 years
(disease modifiers)
Liver cirrhosis
2-5% per year
2-4% per year
Liver failure
Primary liver cancer

HCV and extrahepatic manifestations

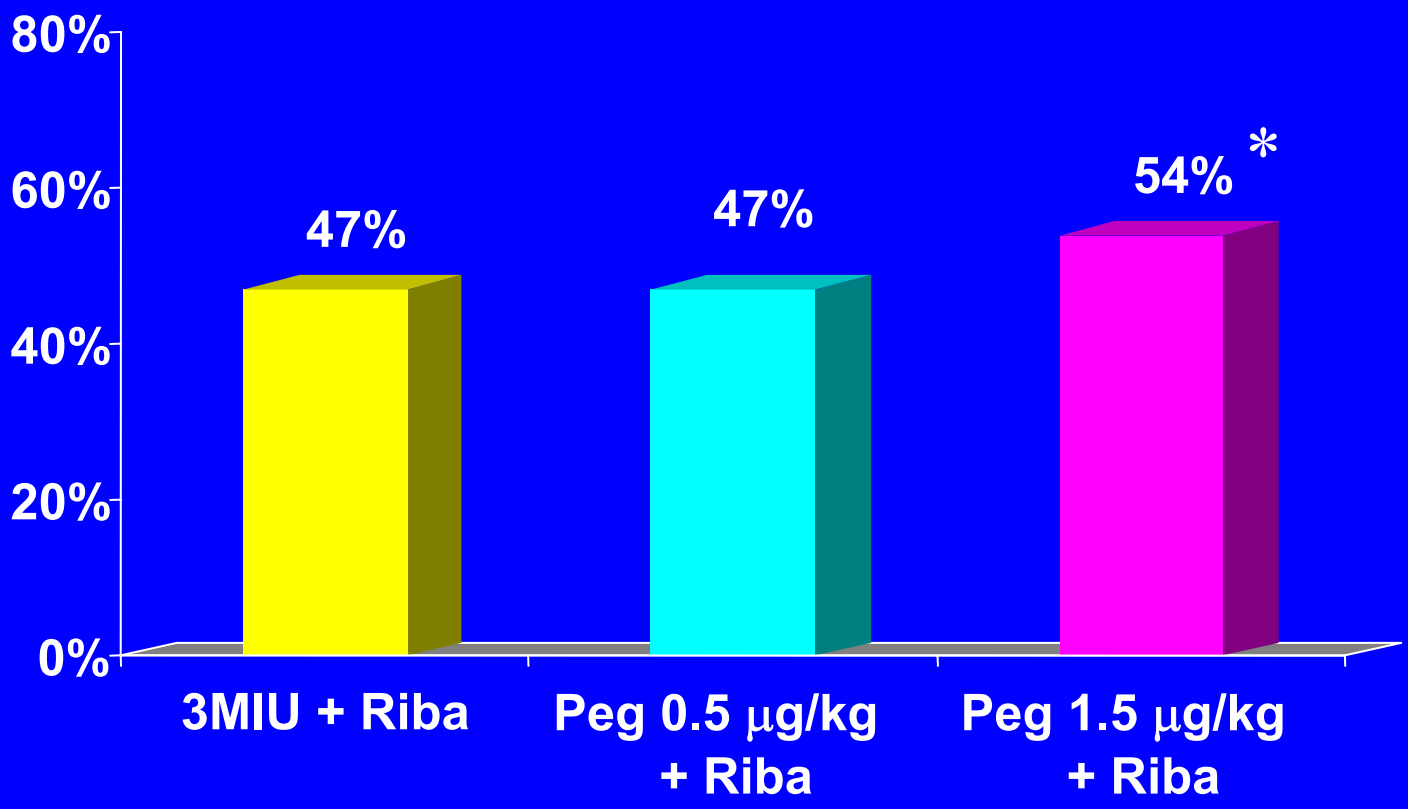


Treatment of Chronic Hepatitis C

- PEG-Interferon-α + ribavirine is superior to standard IFN-α combination or (PEG)-IFN-α alone
- Patients with genotype 1: PEG-IFN-α + ribavirine for 48 weeks
  - $\approx$ 51% SVR rate
- Patients with genotypes 2 and 3: PEG-IFN-α + ribavirine for 24 weeks
  - $\approx$ 80 % SVR rate

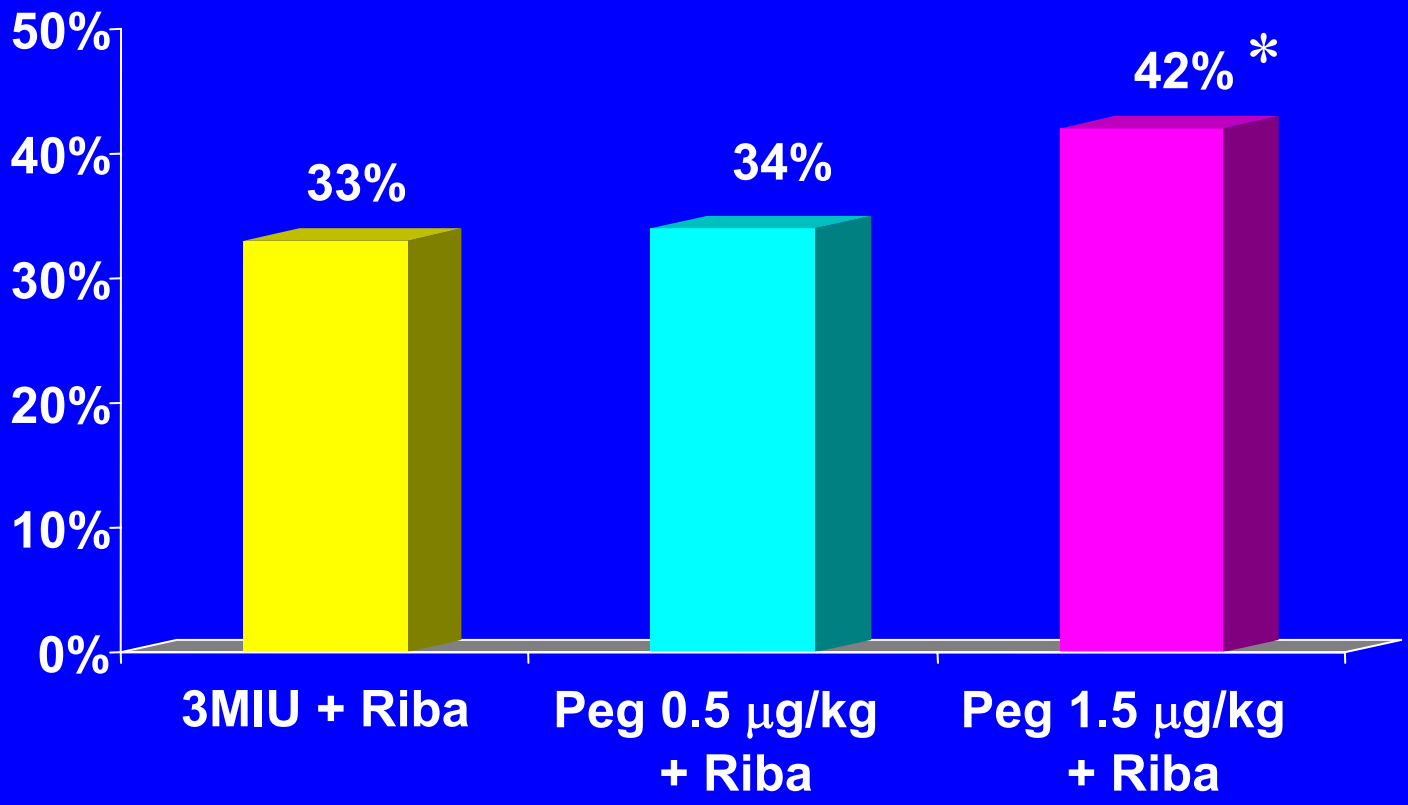
NIH Consensus on Hepatitis C, 2002

PegIntron + Rebetol
Sustained Virologic Response - All Genotypes



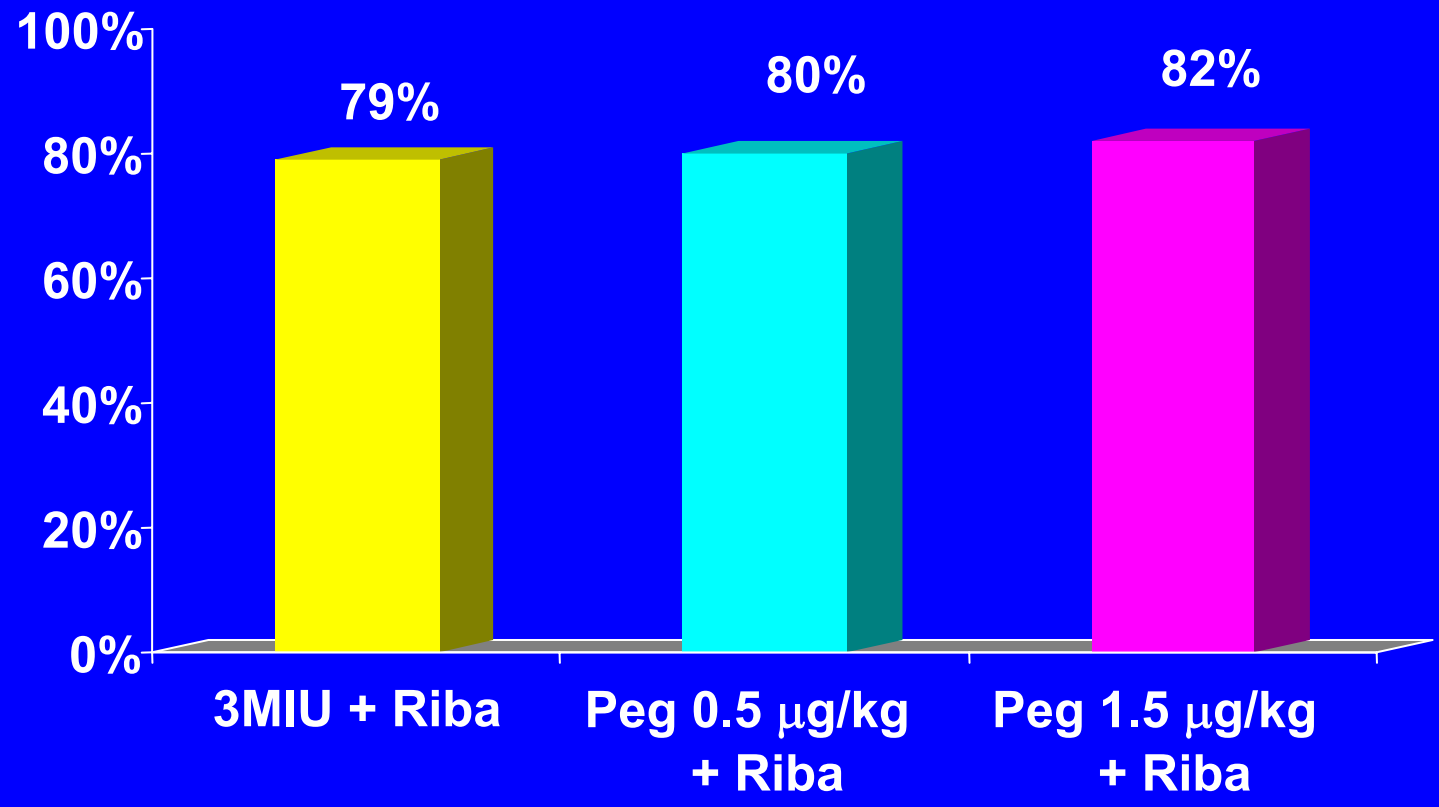
* Peg 1.5/800 vs. I/R p=0.01

PegIntron + Rebetol
Sustained Virologic Response - Genotype 1

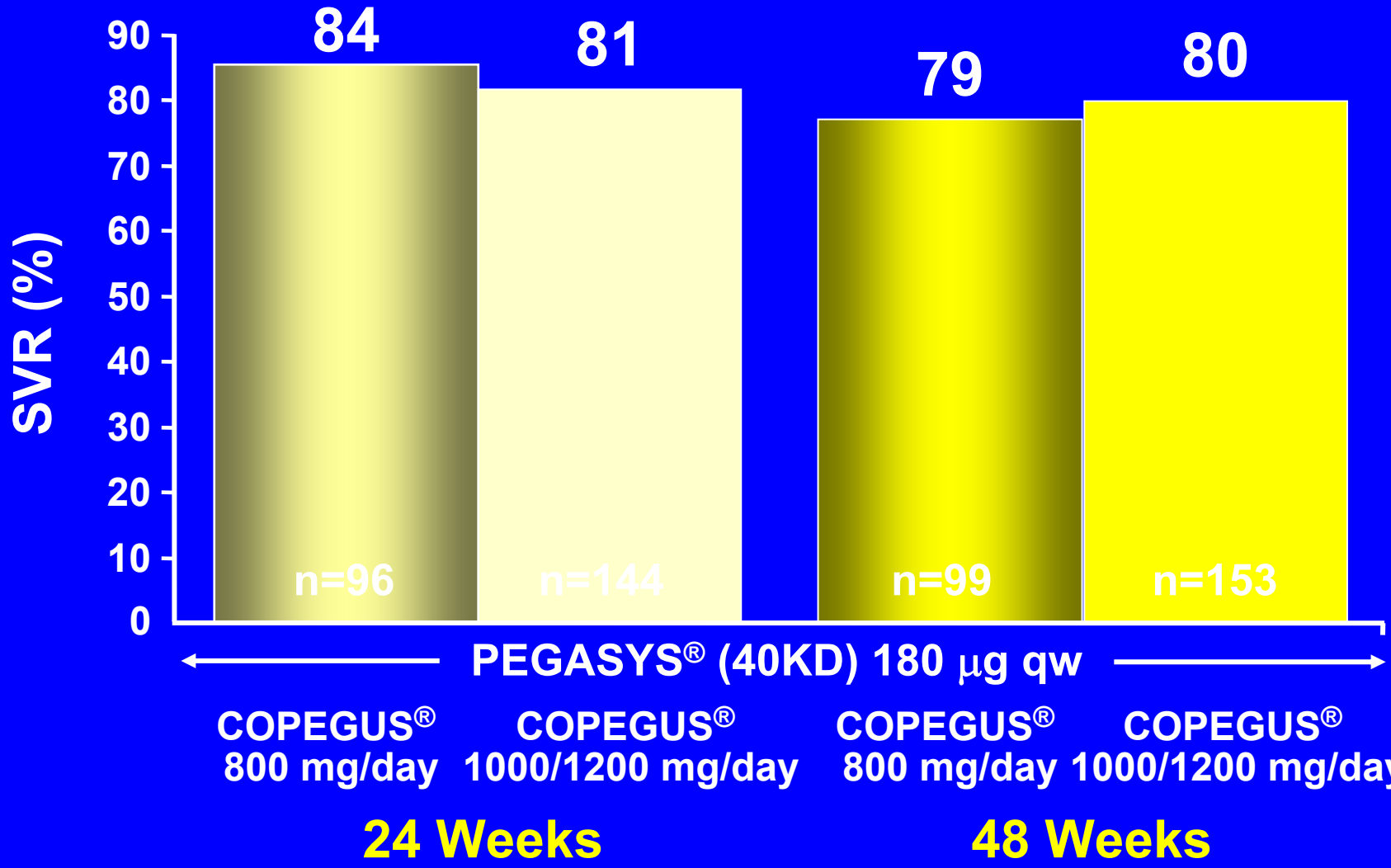


* Peg 1.5/800 vs. I/R p=0.02

PegIntron + Rebetol
Sustained Virologic Response - Genotype 2/3



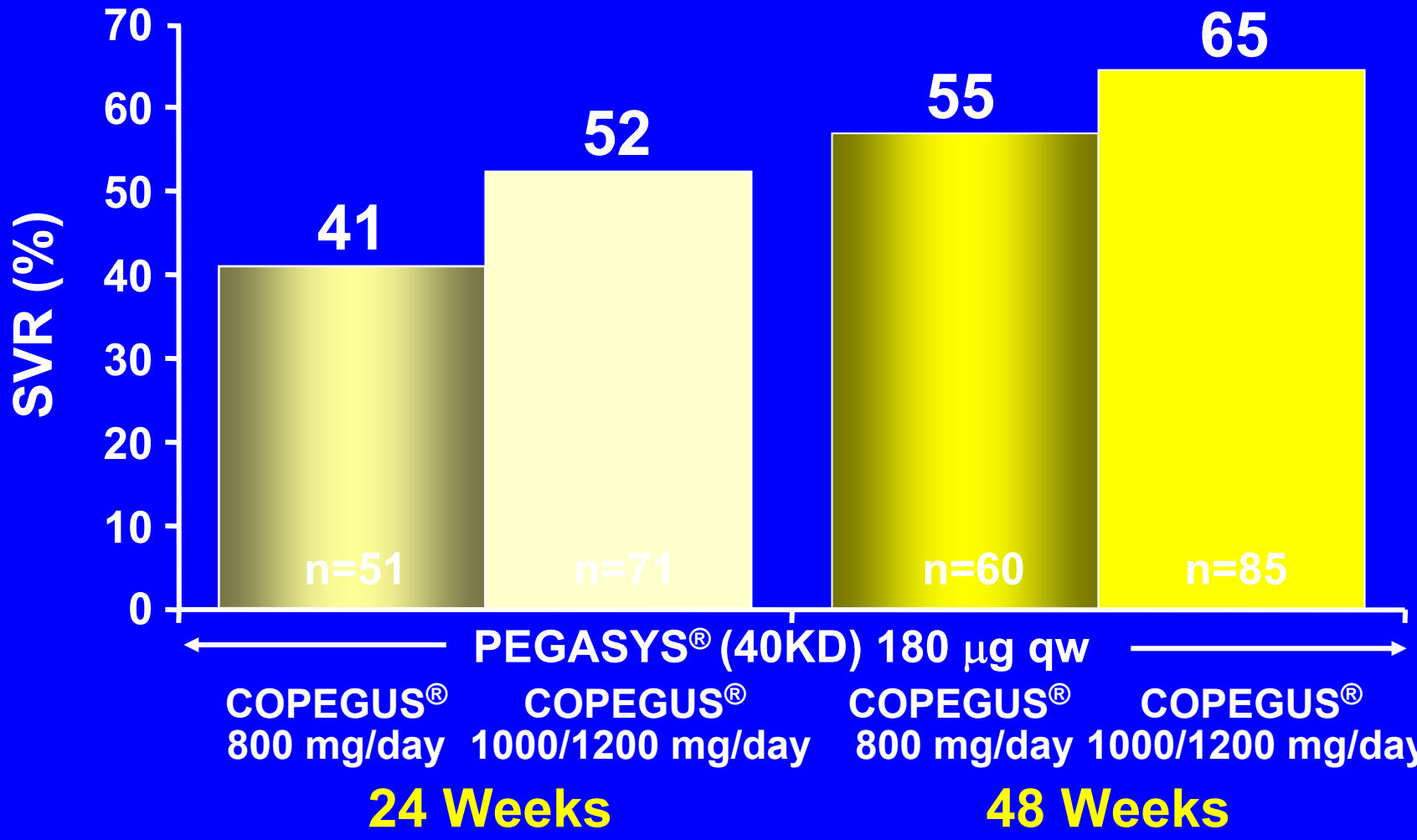
PEGASYS® (40KD) Plus COPEGUS®:
SVR in Patients With HCV Genotype 2 or 3 (ITT Analysis)*



*Intent-to-treat analysis.

Hadziyannis et al. *Ann Intern Med*. 2004.

PEGASYS® (40KD) Plus COPEGUS®:
SVR in Patients With HCV Genotype 1 and Low Viral Load*



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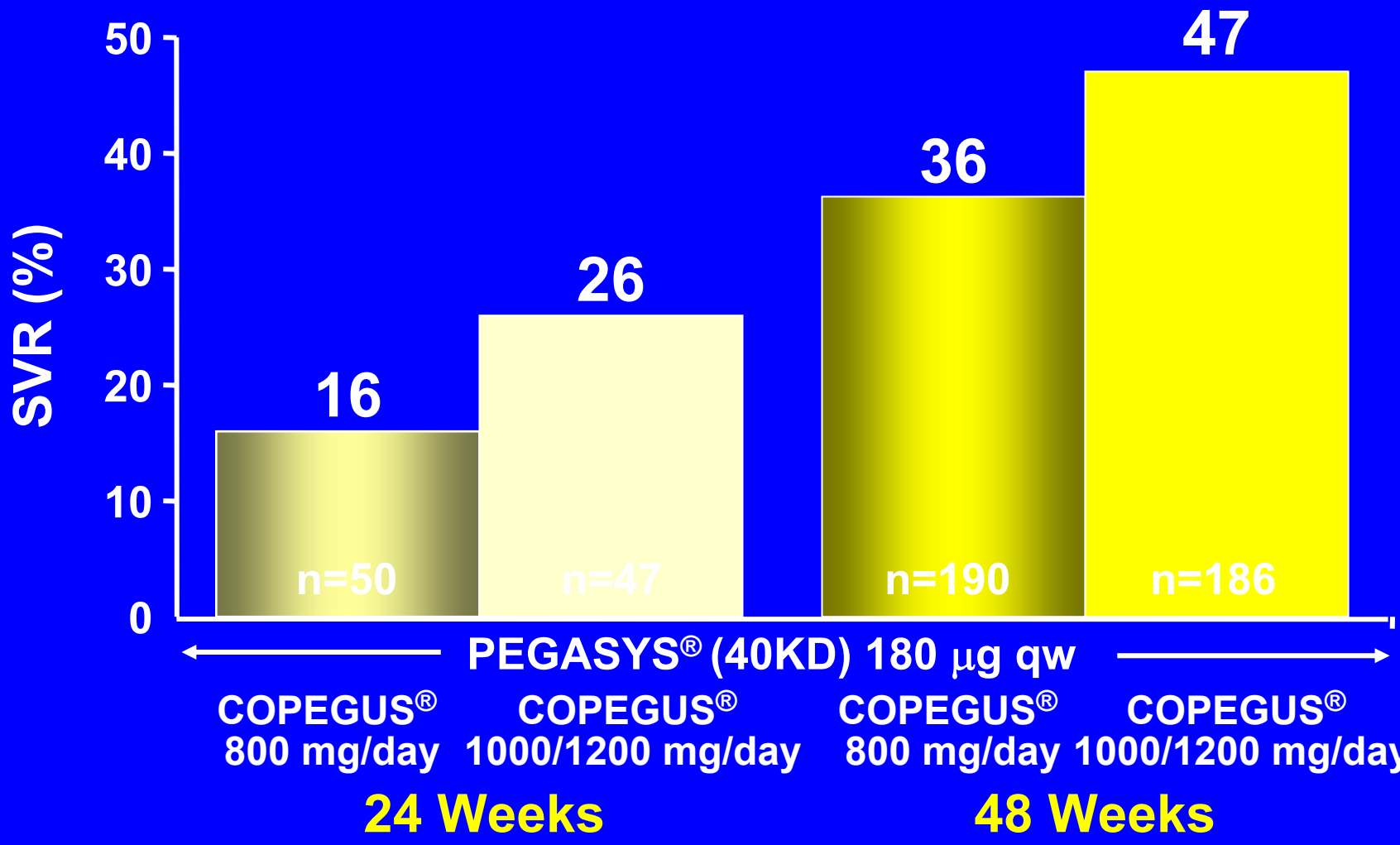
Hadziyannis et al. *Ann Intern Med*. 2004.

PEGASYS® (40KD) Plus COPEGUS®:

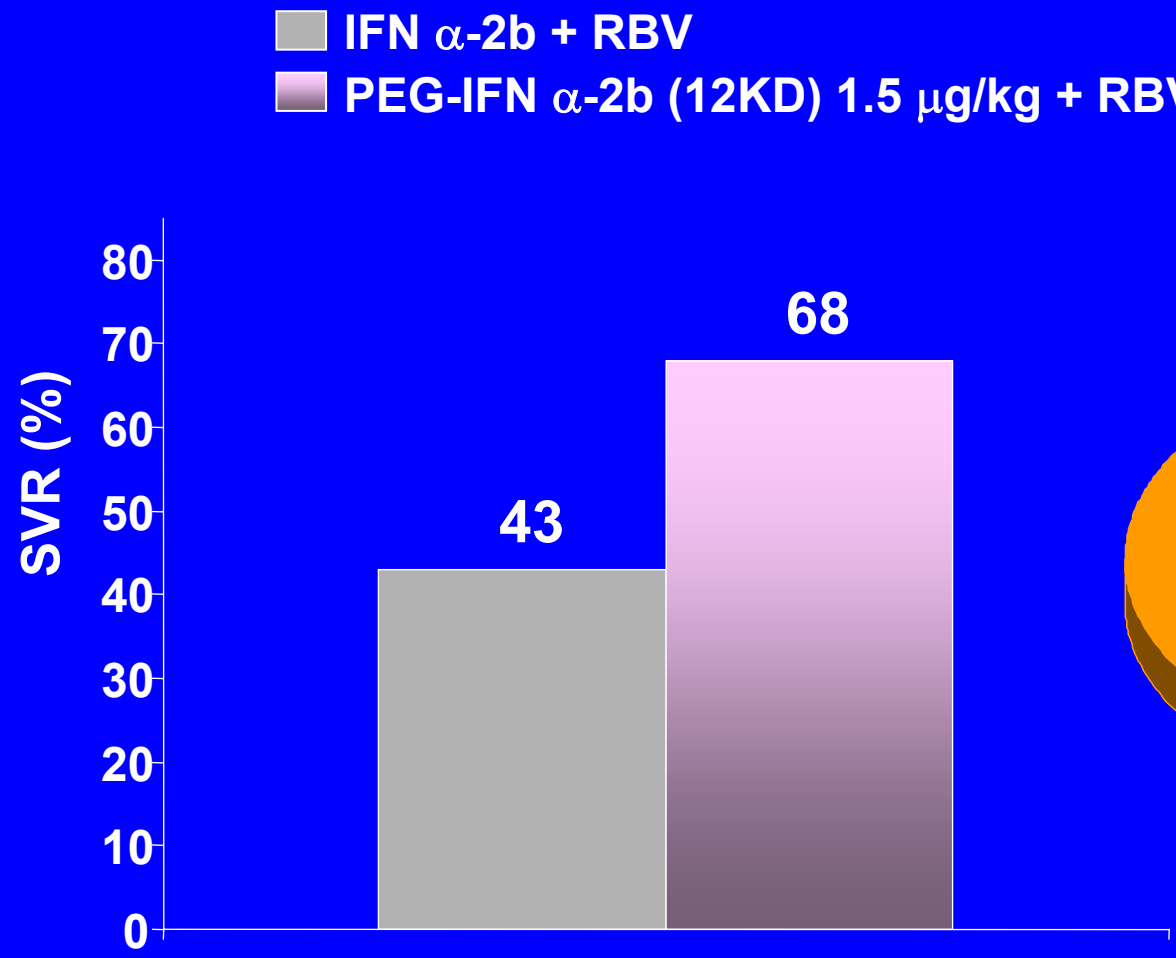
SVR in Patients With HCV Genotype 1 and High Viral Load*

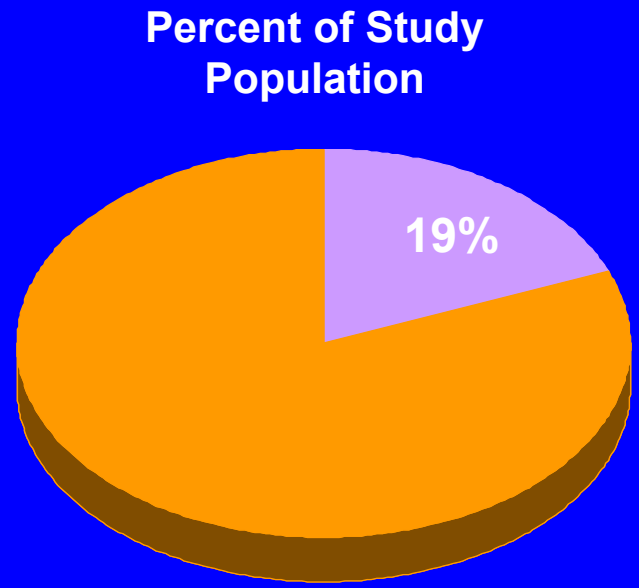


*Intent-to-treat analysis.

Hadziyannis et al. *Ann Intern Med*. 2004.

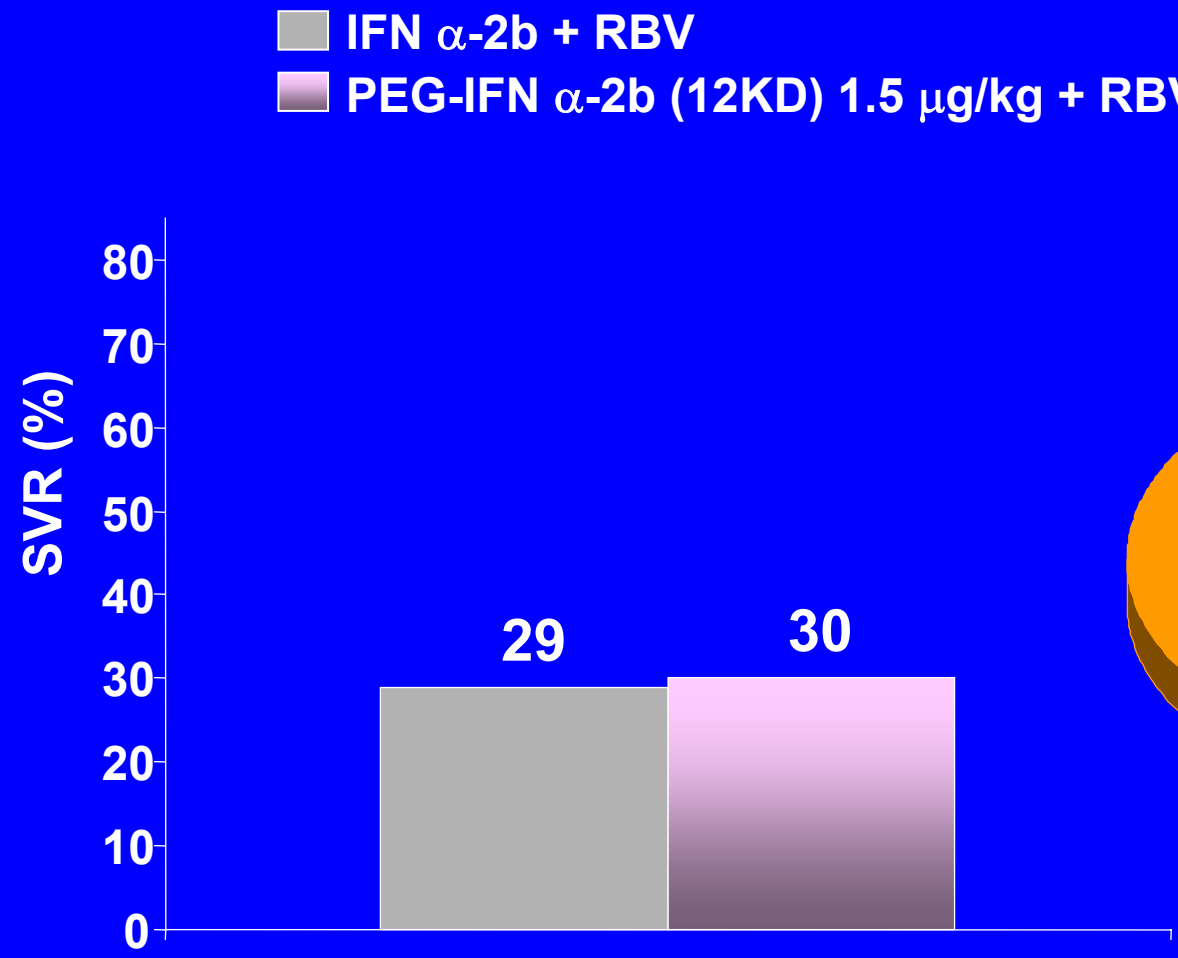
Peginterferon Alfa-2b (12KD) Plus RBV: SVR in HCV Genotype 1 Low Viral Load

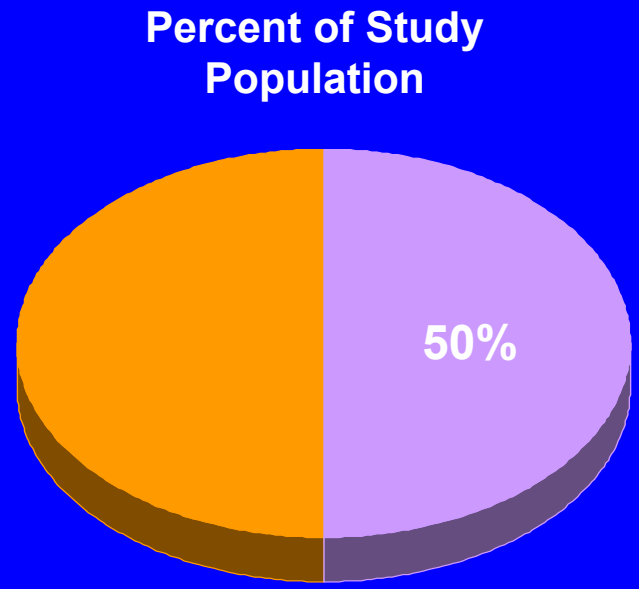




PEG-Intron™. *PDR*®. 56th ed. 2002.

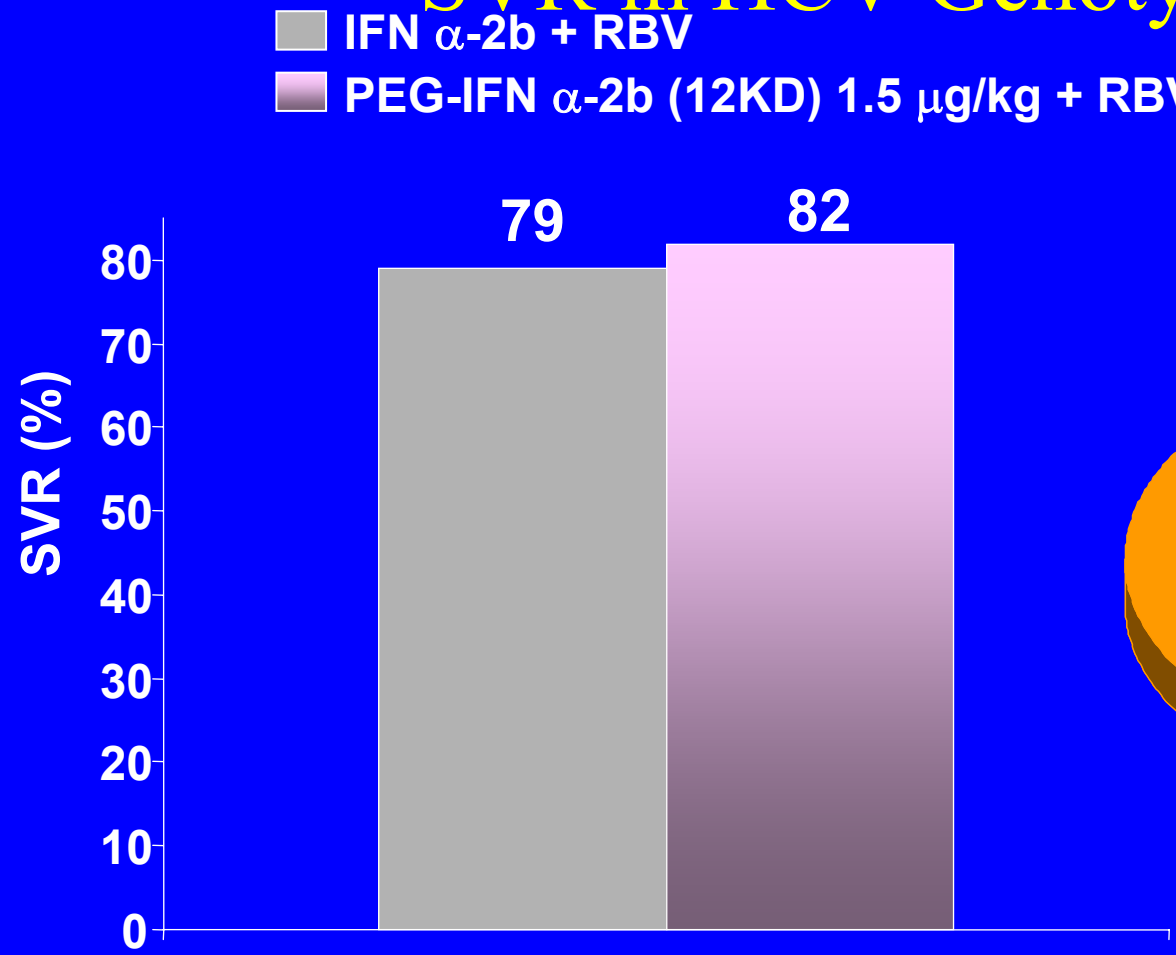
Peginterferon Alfa-2b (12KD) Plus RBV: SVR in HCV Genotype 1 High Viral Load

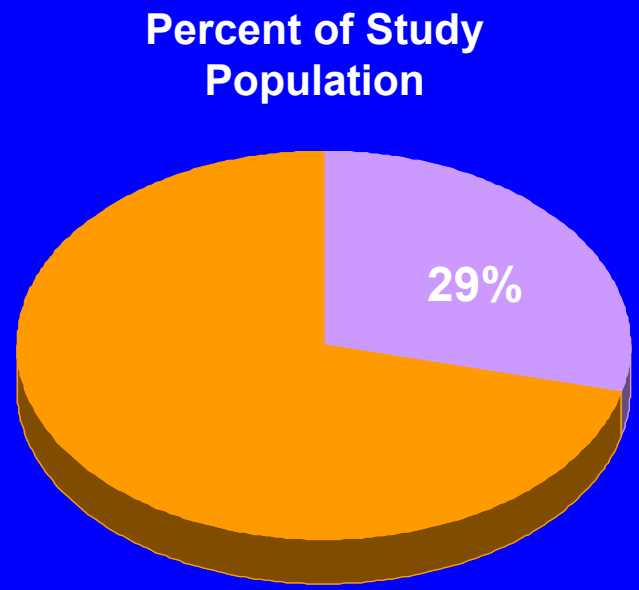




PEG-Intron™. *PDR*®. 56th ed. 2002.

Peginterferon Alfa-2b (12KD) Plus RBV: SVR in HCV Genotype 2/3





PEG-Intron™. *PDR*®. 56th ed. 2002.

Treating Patients with Chronic Hepatitis C: Whom?

- Consider patient's wish, contraindications
- Monitor patients with F0 - F1 (irrespectively of the A score), due to the low risk of progression of liver disease in the absence of cofactors
- Consider treatment of F0 – F1 only if:
  - patient presents with extra-hepatic manifestation (e.g. vasculitis due to cryoglobulinemia)
  - patient is highly motivated and wishes to become virus free
- Treat if the fibrosis score is $\geq$ F2 (irrespectively of the A score)

Factors affecting fibrogenesis and response to therapy in HCV infection

Factor	Affects fibrogenesis	Affects treatment response
Age	Yes	Yes
Sex	Yes	Yes
Genotype	Unclear	Yes
Viral load	No	Yes
Alcohol abuse	Yes	Yes
HIV coinfection	Yes	Yes
HBV coinfection	Yes	Unclear
Overweight	Yes	Yes
Steatosis	Yes	Yes
Insulin resistance	Yes	Yes

Final Week-72 Results of APRICOT: A Randomized, Partially Blinded, International Comparative Trial of Peginterferon alfa-2a (40 kDa) (PEGASYS®) ± Ribavirin (COPEGUS®) vs Interferon alfa-2a + Ribavirin in the Treatment of HCV in HIV-HCV Co-infection

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University of California, San Diego

HIV-HCV Co-infection Study

AIDS

PEGASYS®

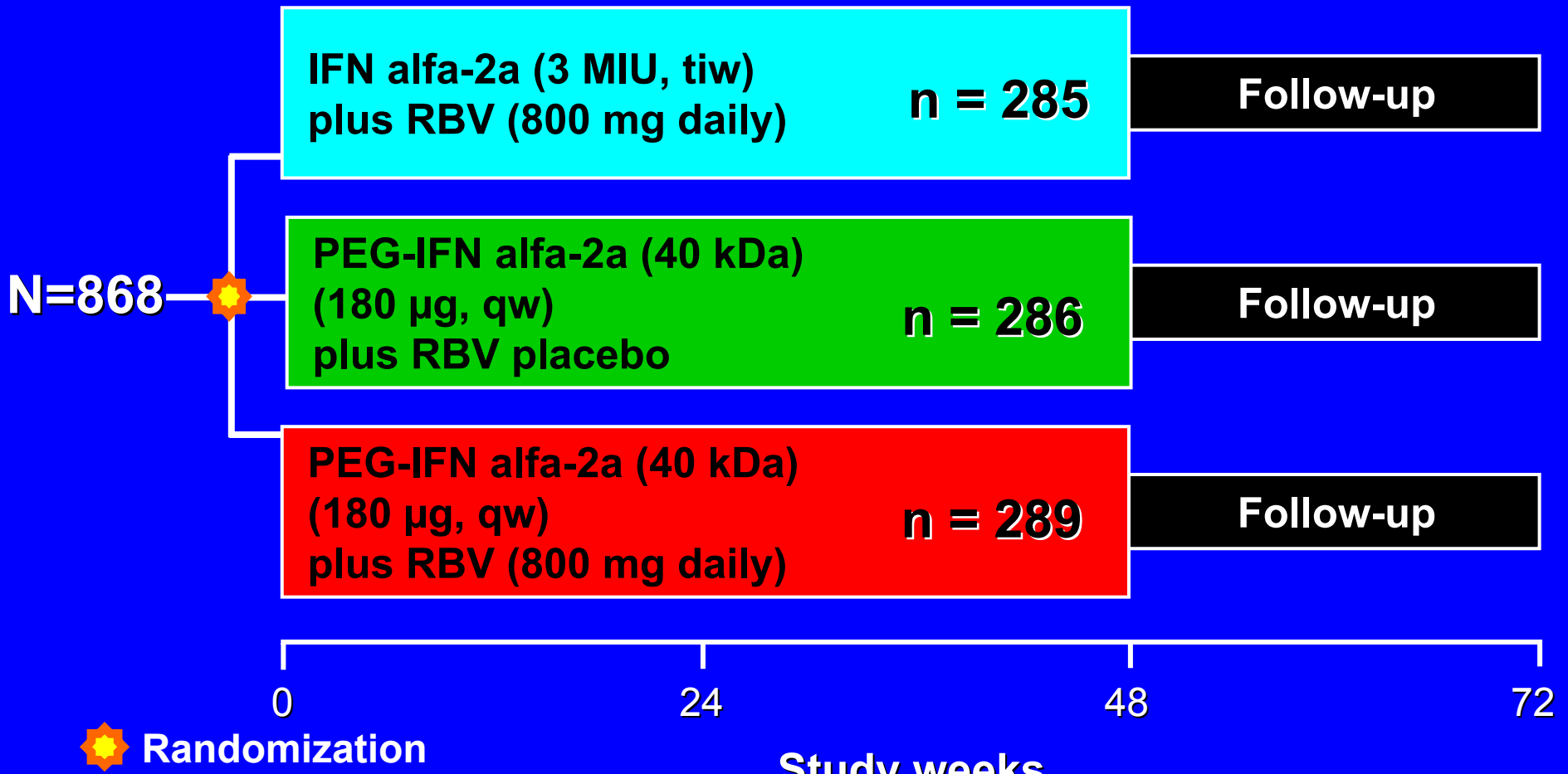
Ribavirin

International

CO-Infection

Trial

APRICOT



860 received at least one dose

APRICOT Study Design

- Use of RBV was blinded in the PEG-IFN alfa-2a (40 kDa) arms (RBV vs placebo)
- Stratified
  - Genotype 1 vs non-1
  - $CD4^+$ 100 to <200/μL vs ≥200/μL
  - ART vs no ART
  - Cirrhotic vs non-cirrhotic
  - Geographic region

Key Inclusion Criteria

- HIV criteria
  - HIV antibody or quantifiable HIV RNA
  - $CD4^+$ cell count
    - ≥200/μL *or*
    - ≥100/μL to <200/μL with <5000 copies/mL HIV RNA
  - Stable HIV disease with or without antiretroviral treatment

Key Inclusion Criteria

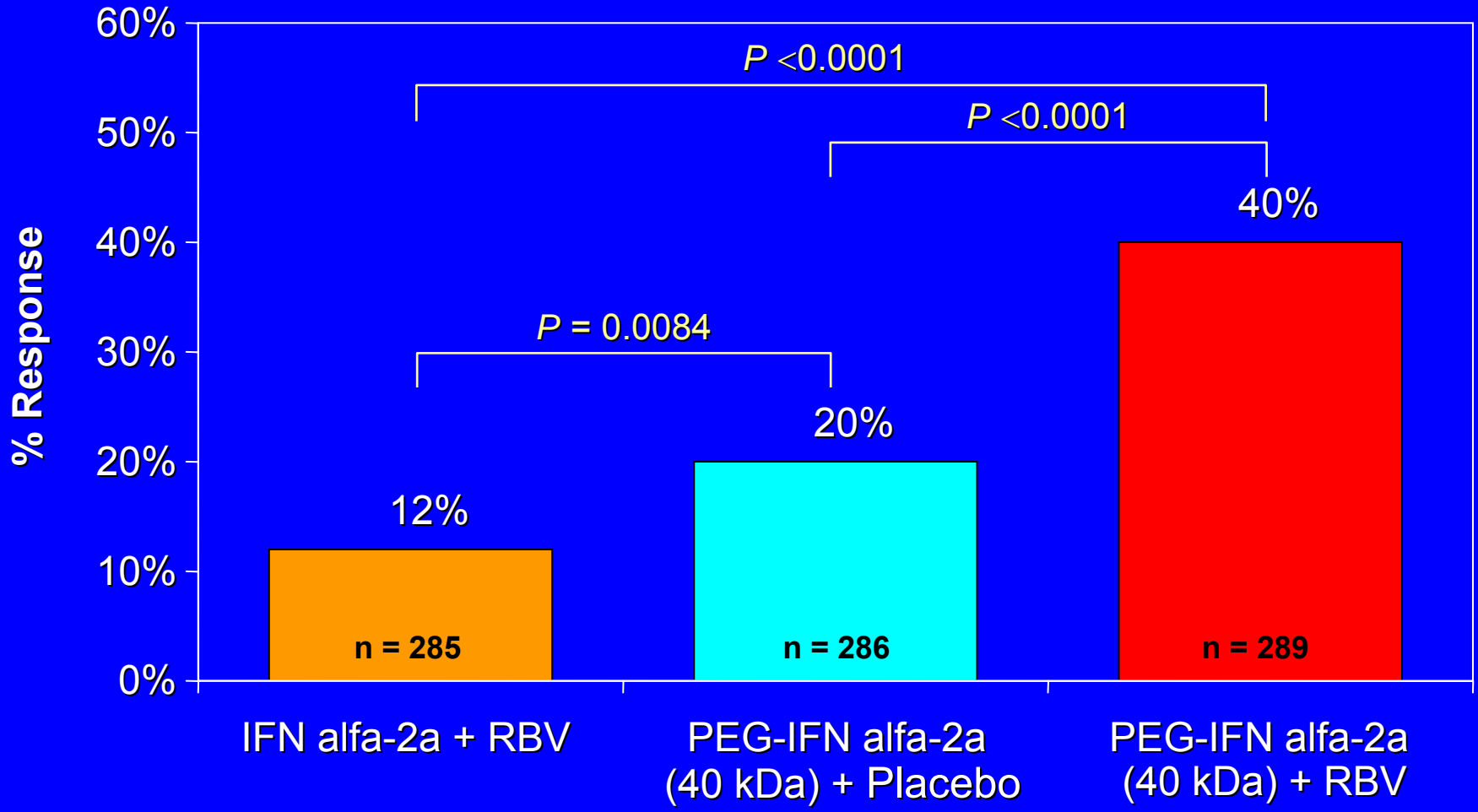
- HCV criteria
  - Naive to IFN and ribavirin
  - HCV antibody positive
  - Quantifiable HCV RNA (Amplicor® MONITOR)
  - Elevated serum ALT
  - Liver biopsy (≤15 months) consistent with HCV infection
  - Non-cirrhotic or cirrhotic
    - If cirrhotic, Child-Pugh Grade A

Primary efficacy endpoint

Sustained Virologic Response (SVR) –
Undetectable serum HCV RNA*
at end of 24-week treatment-free follow-up
(week 72)

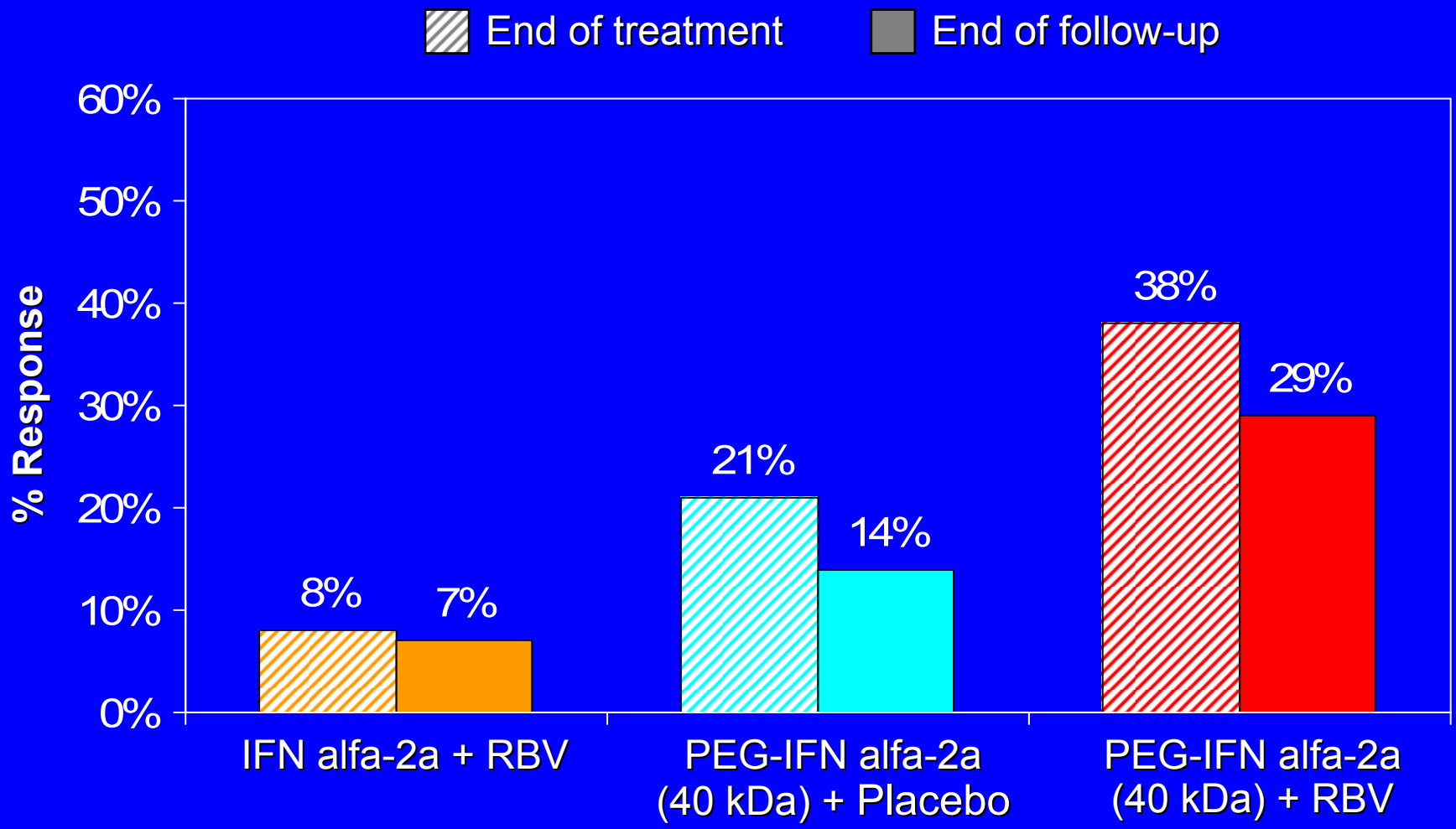
***Cobas Amplicor® HCV test v2.0, sensitivity <50 IU/mL**

Sustained Virologic Response*



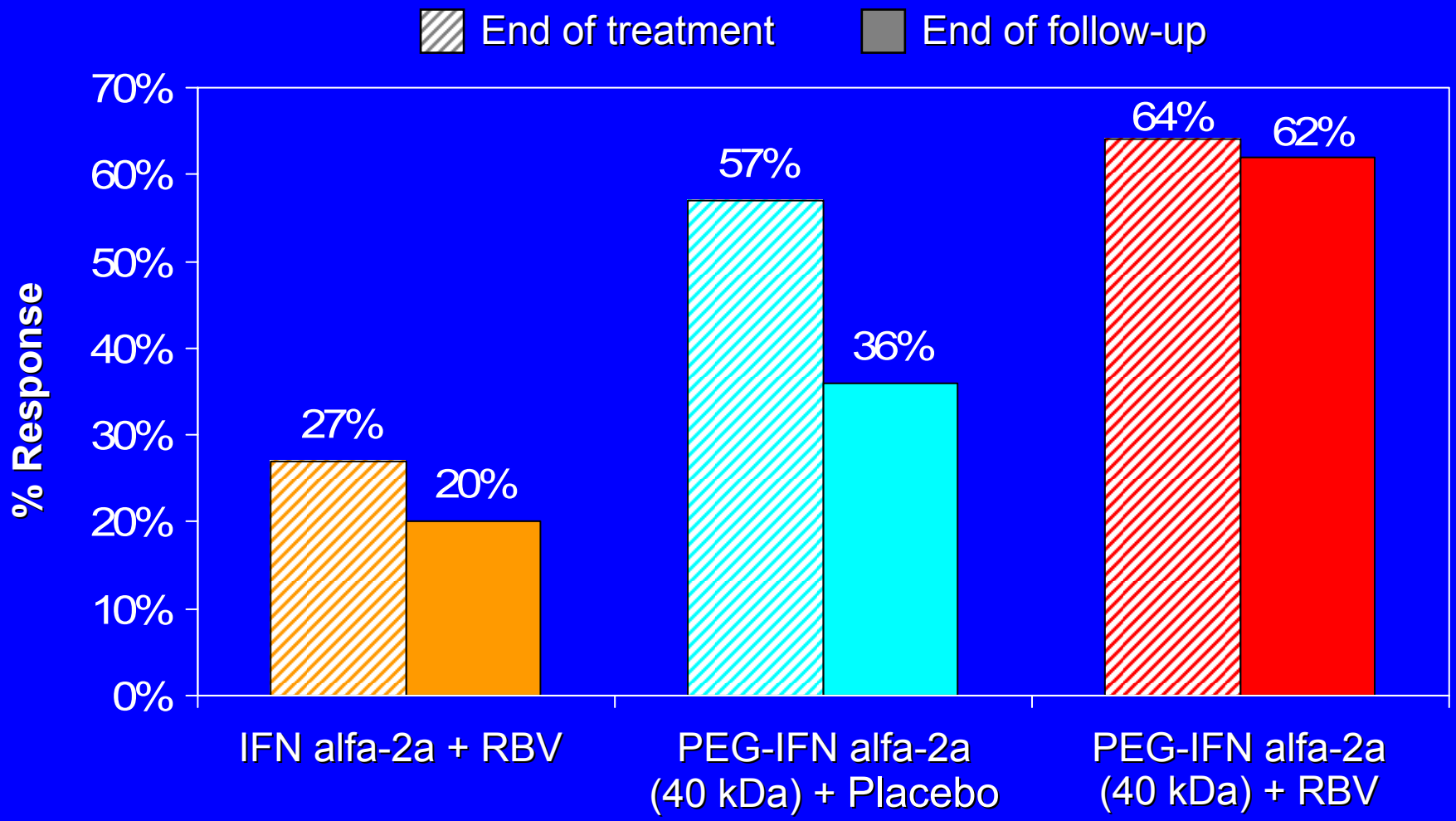
* Defined as <50 IU/mL HCV RNA at week 72; ITT

Virologic Response* – End of Treatment vs End of Follow-up (Genotype 1)



* Defined as <50 IU/mL HCV RNA

Virologic Response* – End of Treatment vs End of Follow-up (Genotype 2 and 3)



* Defined as <50 IU/mL HCV RNA

Treatment of hepatitis C: conclusions

- Only a minority of chronic hepatitis C patients will progress to cirrhosis, depending on the presence of several disease modifiers

- Current treatment options are limited, poorly accepted by patients, and should be offered only to potential « progressors »

- HCV eradication is possible in more than half of patients who complete therapy

Protease Inhibitor: SCH 503034 Monotherapy

- Randomized, double-blind trial
  - HCV-positive patients who failed PegIFN, N = 61
- Randomized to:
  - 100 mg BID
  - 200 mg BID
  - Placebo
  - 400 mg BID
  - 400 mg TID
- Reduction in HCV VL corresponded with dosage
- Mean maximum VL reduction in 400 mg TID group
  - 2.06 $\log_{10}$ from baseline (range, 1.1-2.7 $\log_{10}$)

Zeuzem F, et al. AASLD 2005. Abstracts 94, 201.

SCH 503034 + PegIFN alfa-2b

- Multicenter, open-label study in HCV-positive patients who failed PegIFN alfa, N = 61
- Random sequence with 3-week washout between treatments:
  - SCH 503034 200 mg or 400 mg TID for 7 days
  - PegIFN-alfa 2b 1.5 µg/kg/QW for 14 days
  - Combined therapy for 14 days
- HCV RNA undetectable:
  - 400 mg combination group: 4/10
  - PegIFN alfa-2b alone: 0/22
- Mean maximum VL reductions:
  - 200 mg combination group: 2.4 $\log_{10}$ copies/mL
  - 400 mg combination group: 2.9 $\log_{10}$ copies/mL

Zeuzem F, et al. AASLD 2005. Abstracts 94, 201.

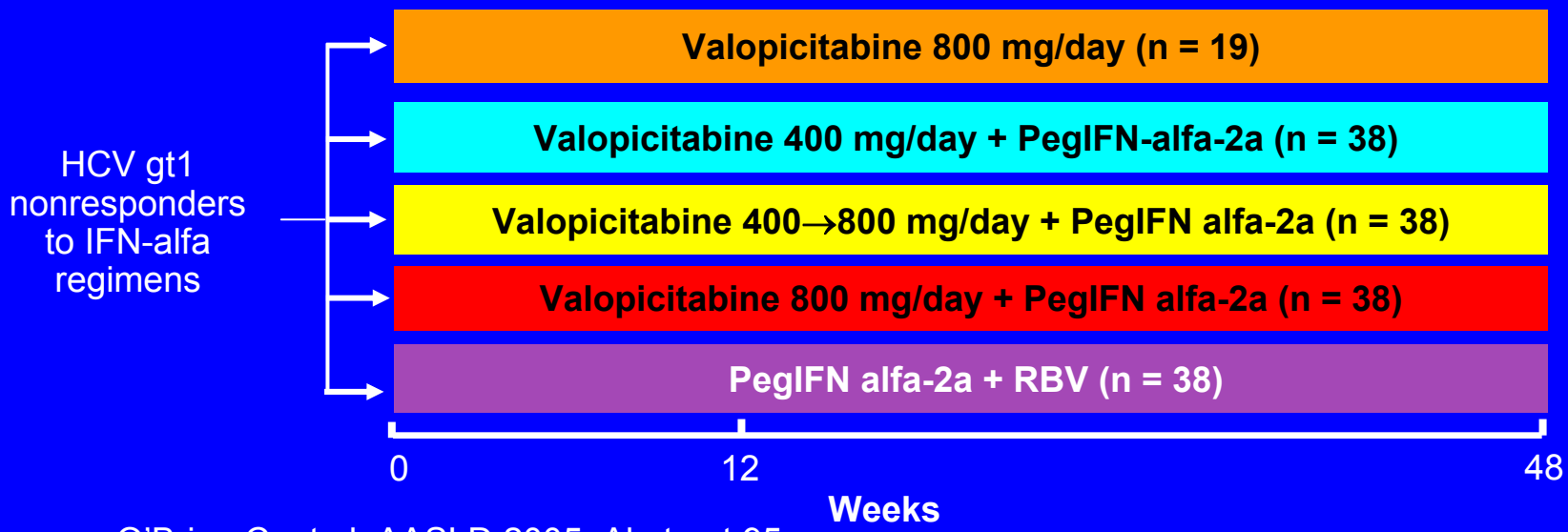
Protease Inhibitor: VX-950 Phase 1b Trial

- Subjects:
  - Healthy HCV-negative (3 panels of 8 subjects)
  - HCV genotype 1 (3 panels of 12 subjects)
- Dosing:
  - Part A: 450 mg, 750 mg, 1250 mg Q8h for 5 days
  - Part B: 450 mg or 750 mg Q8H or 1250 mg Q12h for 14 days
- All HCV-positive patients demonstrated ≥ 2 $\log_{10}$ viral load decline
- 750-mg dose group (highest trough concentration):
  - 4.4 $\log_{10}$ decline in HCV RNA

Reesink HW, et al. AASLD 2005. Abstract LB06.

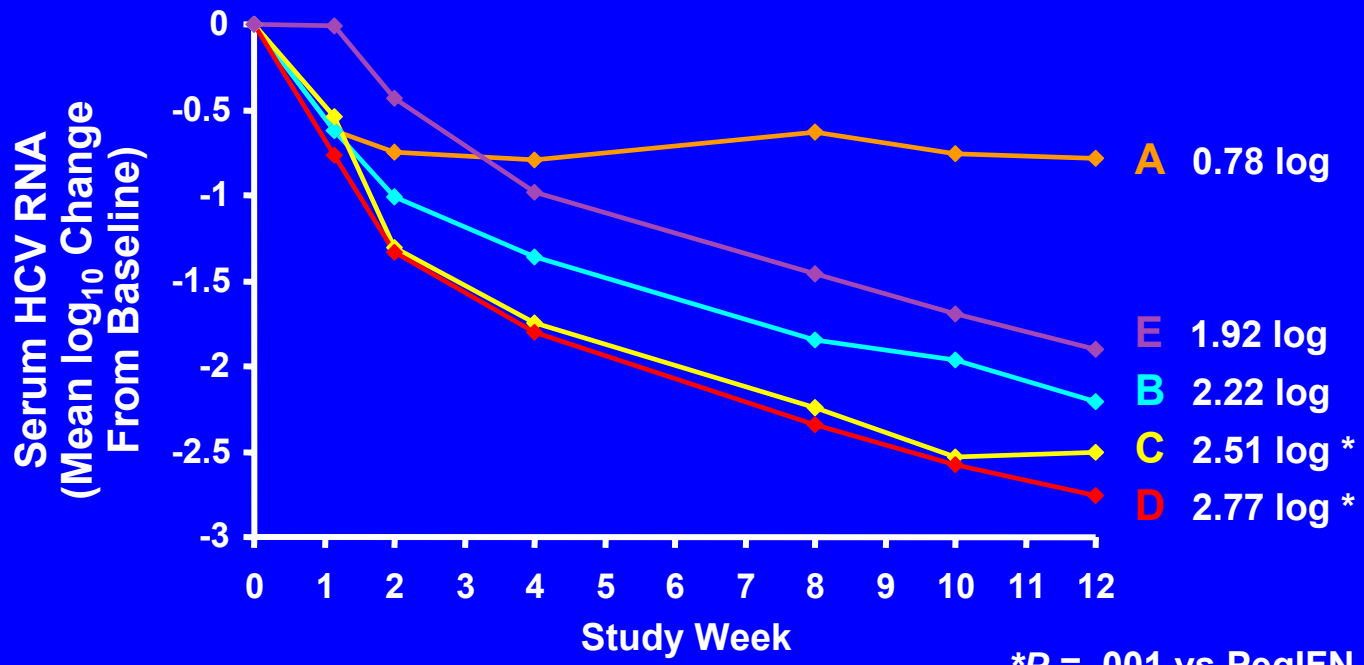
Ribonucleoside Analogue Prodrug: Valopicitabine

- Multicenter (22), randomized, controlled trial in HCV gt1 nonresponders
- HCV RNA response criteria at Weeks 4, 12, 24
  - Patients required to have HCV RNA drop ≥ 0.5 log at Week 4, ≥ 1.0 log at Week 12, and > 2.0 log at Week 24 to continue treatment
  - Early termination if viral response criteria not met
- Primary efficacy endpoint: SVR 6 months after last dose of study medicine



O'Brien C, et al. AASLD 2005. Abstract 95.

HCV RNA Reduction at Week 12 With Valopicitabine



*P = .001 vs PegIFN + RBV

A Valopicitabine 800 mg QD
B Valopicitabine 400 mg QD + Peg-IFN 180 µg QW
C Valopicitabine 400-800 mg QD → 800 mg QD + Peg-IFN 180 µg QW
D Valopicitabine 800 mg QD + Peg-IFN 180 µg QW
E Peg-IFN 180 µg QW + Ribavirin BID

O'Brien C, et al. AASLD 2005. Abstract 95.

New Agents: Summary

Antiviral	Manufacturer	Drug Category	Phase of Development
Valopicitabine	Idenix	Ribonucleoside analogue prodrug	Phase 2b
Albuferon	Human Genome Sciences	IFN-alfa fused to HSA	Phase 2
HCV-AB^{XTL}	XTL	Monoclonal Ab (anti-E2)	Phase 1/2
VX-950	Vertex	Protease inhibitor	Phase 1b
SCH 503034	Schering	Protease inhibitor	Phase 1
GNS 037	Genoscience	Entry inhibitor	Preclinical
ITMN A and B	Intermune	Protease inhibitors	Preclinical